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PHASE III STUDIES

Bendamustine versus chlorambucil in treatment of chronic lymphocytic leukaemia in China: a randomized, open-label, parallel-controlled, phase III clinical trial

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Summary

Background. Chronic lymphoblastic leukemia (CLL) is the most common adult leukemia and mainly affects the elderly. Chemoimmunotherapy still has a role in the standard frontline therapy for specific population. However, the clinical activity of bendamustine has not been investigated in unfit Chinese patients with CLL. This study aimed to compare the efficacy and safety of bendamustine versus chlorambucil for untreated Chinese patients with Binet stage B/C CLL. *Methods.* In this multi-center, randomized, open-label, parallel-controlled, phase III trial, patients with previously untreated CLL were enrolled and randomly assigned (1:1) to receive bendamustine or chlorambucil. The primary endpoint was the objective response rate. Secondary endpoints included progression-free survival, the duration of response, and overall survival. Adverse events were recorded to evaluate safety. *Results*. Of 158 screened patients, 147 were enrolled and randomly allocated to receive bendamustine (n = 72) or chlorambucil (n = 75). After a median follow-up of 25.6 months (IQR 12.5–27.7), 69.0% (95% CI, 56.9–79.5) of bendamustine-treated patients achieved objective response and 37.0% (95% CI, 26.0–49.1) of chlorambucil with a difference of 32.0% (95%CI: 16.6–47.5), demonstrating the superiority of bendamustine to chlorambucil ($p < 0.001$). The median progression-free survival was longer for bendamustine (16.5 months; 95% CI, 11.3–24.7) versus chlorambucil (9.6 months; 95% CI, 8.7–11.8; $p < 0.001$). A longer median duration of response was seen in those receiving bendamustine (19.2 months; 95% CI, 11.8–29.1) than chlorambucil (10.7 months; 95% CI, 5.6–13.6; $p = 0.0018$). Median overall survival was not reached in either group. Overall survival at 18 months was 88% for bendamustine versus 85% for chlorambucil. Most common adverse events in both groups were neutropenia and thrombocytopenia. *Conclusion.* In untreated Chinese patients with Binet stage B/C CLL, bendamustine induced the better objective response and resulted in longer progression-free survival than chlorambucil. Overall, these results validate the role of bendamustine as an effective and safe first-line therapy in this population.

Keywords Bendamustine · Chlorambucil · Chronic lymphocytic leukemia · Objective response rate · Progression-free survival

Introduction

Chronic lymphocytic leukemia (CLL) is a malignant tumor of the blood system and the most common type of adult leukemia [16]. The proportion of male patients with CLL is higher than that of female patients and is more common in the elderly [30]. The incidence was 4.6 per 100,000 inhabitants, with 82.6% of patients surviving for 5 years [3]. Despite treatment options for CLL underwent fundamental changes due to the introduction of new therapies during the past few years, such as targeted therapies, they were usually complicated by toxic effects and the emergence of resistance [27]. Notably, although durable remissions were induced in many patients with these agents, clinical relapses occur and can be very difficult to manage, especially in high-risk patients [33]. Meanwhile, these advances in current

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therapies do not benefit all patients with CLL uniformly due to the highly variable clinical course [4, 11].

For younger, physically fit patients, chemoimmunotherapy (CIT) with fludarabine, cyclophosphamide, and rituximab (FCR) remains the current standard therapy [24]. Although the FCR regimen is efficacious, it is associated with substantial safety concerns, including severe myelosuppression, risk of treatment-related myelodysplasia, and infectious complications [25]. On the contrary, elderly patients typically have comorbidities, making them ineligible for the more intensive fludarabine-based treatment regimen, whereas is appropriate for lower-intensity regimens, including bendamustine and chlorambucil [19]. Additionally, the currently available evidence supports that therapy regimens containing chlorambucil or bendamustine, etc. alternative agents are still the treatment options for first-line therapy in these unfit patients [11].

In western countries, bendamustine has been approved for the treatment of CLL (Binet stage B or C) in patients for whom fludarabine-based chemotherapy is not appropriate [3, 32]. Until 2019, bendamustine was approved by China National Medical Product Administration (NMPA) for the indolent B-cell non-Hodgkin lymphomas (NKL) and has shown clinical activity [26]. Nevertheless, the evidence for the clinical activity of bendamustine against CLL was only from Caucasian patients [2], its effects on the prognosis and quality of life, as well as the safety profile in Chinese patients have not been reported. Especially, CLL mainly affects the elderly [23, 28]; accordingly, the burden of CLL is predicted to increase due to the aging population and the large population base in China. Notably, CLL is extremely rare in Asians [35], leading to very few evidence come from Asian population. Meanwhile, since genetic factors, environmental factors, or both influence the risk and disease conditions of CLL [10, 18], the investigation of bendamustine in the management of Chinese patients with CLL remains needed. In the Chinese Society of Clinical Oncology (CSCO) diagnosis and treatment guidelines for malignant lymphoma (2021), bendamustine is still recommended as the first-line chemotherapy [36]. Accordingly, bendamustine monotherapy remains as the primary choice for most treatment-naïve patients in the Chinese clinical practice. Bendamustine plus rituximab (BR) was recommended only when bendamustine treatment fails. Additionally, the associated costs of CLL therapy cannot be ignored. Even novel agents, such as rituximab, have efficacy or toxicity advantages, long-term treatment with these agents at today's costs would increase the economic burden in Chinese patients, especially in the low-income family [28, 34, 37]. Thus, it is still necessary to investigate the efficacy and safety of bendamustine monotherapy in Chinese patients.

Therefore, the present study reported results of the first multi-center, randomized, phase III trial in Chinese patients with CLL, comparing the efficacy and safety of bendamustine with chlorambucil. This study is the first positive-controlled trial that enrolled previously untreated Chinese patients with Binet stage B/C CLL who are unsuitable for fludarabine-based chemotherapy.

Materials and methods

Study design

This randomized, open-label, parallel-controlled study was conducted between November 25, 2009, and October 19, 2016, with eligible patients recruited from 18 study sites in China. The study was done in accordance with Good Clinical Practice and the Declaration of Helsinki. An institutional review board approved the protocol (Approval number: 2008[27] and 2008[71]-2). All of the participants provided written informed consent. The trial was registered at ClinicalTrials.gov, NCT01109264.

Participants eligibility

Previously untreated patients aged 18 years or older who were diagnosed with Binet stage B or C CLL according to the 2008 International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria were included [6]. All patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 score and a life expectancy of at least 3 months. Patients were required to have adequate organ function (alanine aminotransferase level ≤ 3 times the upper limit of normal [ULN]; aspartate transaminase level ≤ 3 times the ULN; total bilirubin level 2 times the ULN; creatinine clearancerate ≥ 40 ml/min). Patients were also required to have at least one of the following treatment indications, including a platelet count of less than 100×10^9 cells/L, a concentration of hemoglobin (non-hemolytic) less than 100 g/L, lymphadenectasis (the longest diameter > 10 cm).

Patients who had been diagnosed or treated for malignancy other than CLL (including central nervous system lymphoma) within the past 1 year were ineligible. We also excluded patients with immune hemolysis or immune thrombocytopenia who required glucocorticoid therapy. Patients were also ineligible if they had undergone major surgery in the past 30 days or had been treated with other drugs in clinical trials in the past 4 weeks. Patients with severe heart failure, cardiomyopathy, myocardial infarction in the past six months, uncontrolled diabetes, uncontrollable hypertension (After treatment, systolic blood pressure was > 150 mmHg and diastolic blood pressure was > 90 mmHg), serious infection, central nervous system dysfunction with clinical manifestations and allergic to any test drug or mannitol

(excipient) were not allowed to participate. In addition, pregnant women, lactating women, and women of childbearing age who did not use contraception were excluded from the study.

Randomization

All eligible patients were randomly assigned in a 1:1 ratio to the bendamustine group (BEN group) or the chlorambucil group (CLB group) by a computer-generated coding system. Randomization codes were provided by an independent biostatistician before the study began and were done with SAS version 9.4 statistical software (procedure "PROC PLAN"). Patients were stratified by Binet stage (B or C). The study was open-label to investigators and patients. Patients, physicians, and individuals assessing outcomes and analyzed data were not masked to treatment allocation. All data were recorded at the head office.

Procedures

Patients received the assigned treatments (bendamustine or chlorambucil) every 4 weeks (28-day cycle) and up to 6 cycles, until disease progression, unacceptable toxic effects, consent withdrawal, or investigator decision. Bendamustine (Simcere Pharmaceutical Co., Ltd., China) was administered by intravenous infusion over 60 min at a dose of 100 mg/m^2/day on days 1 to 2 every 4 weeks (one cycle). Bendamustine (25 mg/bottle) was provided as a sterile solution and diluted in 250 ml saline prior to infusion. Chlorambucil (GlaxosmithKline, Uxbridge, United Kingdom) was given orally at a dose of 0.4 mg/kg/day on days 1 to 2 and 15 to 16 every 4 weeks. During the chlorambucil administration, the blood routine was monitored weekly. Chlorambucil administration on days 15–16 was to be suspended if white blood cell (WBC) counts at days 14 ± 2 after chlorambucil decreased to below 10×10^9/L; If not, chlorambucil administration continued.

Dose adjustments were allowed according to the adverse events grading. Toxicity was managed with supportive care, pre-specified reductions, or the discontinuation in the doses of drugs until adverse events became tolerable. If patients experienced unacceptable grade 3/4 adverse events, the doses of bendamustine or chlorambucil could be reduced to 50% of initial dose, until to 25 mg/m^2 or 0.1 mg/kg/day. If the patient developed grade 3/4 hematologic toxicity at the third time persisted for more than 4 week, then bendamustine or chlorambucil dosing was terminated. All subjects were assessed for tumor response and progression at the end of the third cycle. Tumor response was assessed based on physical exam, laboratory results, computed tomography or magnetic resonance imaging, and bone marrow evaluation according to 2008 iwCLL criteria. The images were centrally reviewed and assessed by the independent review committee. For subjects with complete response or partial response, two additional cycles for a maximum of six cycles in total were recommended. Subjects who were assessed for disease progression discontinued treatment. The curative effect was evaluated again at the end of the fifth or sixth cycle. Subjects were followed up every 3 months after the end of treatment, with a maximum follow-up period of 2 years after randomization or when disease progression was observed in 80% of subjects.

Outcomes

The primary endpoint was objective response rate, defined as the proportion of patients who achieved a complete response or partial response. Secondary endpoints included progression-free survival, the duration of response, overall survival. Progression-free survival was defined as the time from treatment initiation to disease progression or death from any cause. The duration of remission was defined as the time from initial record to disease remission to the first record to disease progression. Overall survival was defined as the time from randomization to death.

Adverse events (AEs) were recorded to evaluate safety. AEs were considered as serious (SAEs) if they resulted in any following conditions: death, a life-threatening AEs, a congenital anomaly/birth defect, a persistent or significant incapacity or organ damages, in-patient hospitalization or prolongation of existing hospitalization, a significant medical event that require intervention. Drug-related AEs were defined as AEs that classified as possibly, probably, or definitely related to investigational drugs. Significant AEs were defined as AEs that led to dose reduction, interruption, or discontinuation, other than a serious AE. Adverse reactions (ADRs) were defined as AEs that classified as definitely or possibly related to investigational drugs.

Statistical methods and sample size calculation

The sample size calculation for this superiority trial was based on published data [13]. The main statistical assumption of this study was that the objective response rate in the experimental arm would be superior to that in the control arm under the selected superiority margin (25%). Assuming a 40% objective response rate for chlorambucil in this study, and a 25% increase in the objective response rate of bendamustine to chlorambucil, the necessary enrollment number was calculated to be 60 per group, with a statistical power of 80% and a two-sided type I error of 5% ($\alpha = 0.05$). Allowing for a 20% dropout rate, the recruitment target was 144 participants (72 per group).

Efficacy analyses were performed in the intention-to-treat (ITT) population, which defined as all randomized subjects

who received at least one dose of study drug and at least one efficacy assessment. Per-protocol set was defined as randomized subjects who have completed the prescribed treatment or who have not seriously violated the trial protocol. Per-protocol set was used in a sensitivity analysis confirming robustness of the data. Safety assessment was analyzed in the safety analysis set, which consisted of patients who received at least one dose of study drug and had a post-drug safety record.

Analyses were performed using SAS (version 9.4, SAS Institute Inc, Cary, NC, USA). All tests were two-tailed with a multiple significance level of $\alpha = 0.05$. The continuous variables were presented as the number of subjects, mean, standard deviation, median, minimum, and maximum. The categorical variables are presented as number and frequency. The comparison of baseline indexes between groups was performed by analysis of variance, Wilcoxon rank-sum test, or Fisher's exact test. Fisher's exact probability method was used to compare the primary endpoint between groups. Secondary endpoints were analyzed by Kaplan–Meier curves and expressed as median values with 95% confidence intervals (CI). For safety analysis, a statistical description of adverse events was performed. Fisher's exact probability was used to compare the incidence of adverse events between the two groups.

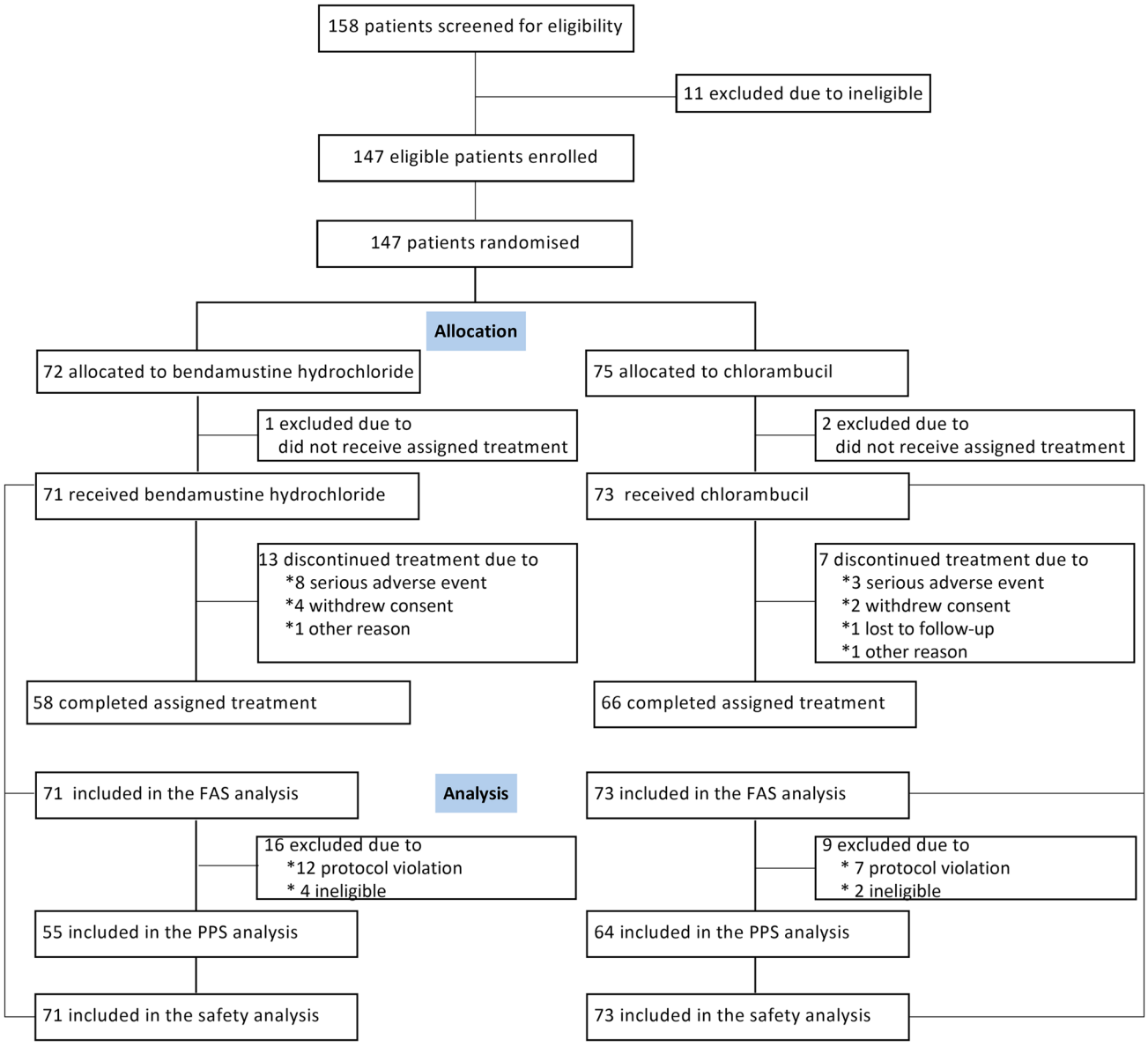

Fig. 1 Flowchart of subjects included in the randomized controlled trial

Results

Patient characteristics

Of the 158 patients screened, 147 were eligible and randomly assigned to treatment (Fig. 1). There were 72 patients randomized to bendamustine therapy and 75 subjects to chlorambucil therapy. Finally, 124 patients completed this study (BEN group, n = 58; CLB group, n = 66). The reasons for not completing the study were intolerance adverse events (BEN, n = 8; CLB, n = 3), consent withdraw (BEN, n = 4; CLB, n = 4), loss to follow-up (BEN, n = 0; CLB, n = 1), and other reasons (BEN, n = 2; CLB, n = 1). A total of 144 patients were included in efficacy and safety analysis (BEN, n = 71; CLB, n = 73). 3 subjects were excluded because they did not receive treatment (BEN, n = 1; CLB, n = 2). Furthermore, 119 subjects were included in per-protocol set (BEN group: n = 55; CLB group: n = 64). 28 subjects were excluded because of at least one protocol violation (BEN group: n = 17; CLB group: n = 11).The baseline characteristics of the two groups were shown in Table 1. Two groups were also well balanced with regard to age, sex, ECOG performance status, Binet stage, and biological characterization of patients.

The median number of treatment cycles was 6 cycles in two groups. Six cycles of treatment were completed by 42 (59.2%) patients in the BEN group and by 52 (71.2%) patients in the CLB group. The median follow-up time of all subjects was 25.6 months (IQR 12.5–27.7). The median relative dose intensity was 98.7% (range, 70%-110%) for BEN and 98.6% (range, 79%-106%) for CLB. Overall, 37 subjects (52.11%) in the BEN group and 4 (5.48%) in the CLB group required at least one dose reduction.

Efficacy

Tumor response

In the ITT population, the objective response rate was 69.0% (95%CI: 56.9–79.5) in the BEN group and 37.0% (95% CI: 26.0–49.1) in the CLB group (Table 2). The difference in rate (BEN group vs. CLB group) was 32.0% (95%CI: 16.6–47.5), demonstrating the superiority of bendamustine to chlorambucil ($p < 0.001$). Among them, 20 (28.2%) patients in the BEN group achieved a complete response and 3 (4.1%) in the in the CLB group. The median duration of response in those receiving bendamustine (19.2 months; 95%CI: 11.8–29.1) was significantly longer than that receiving chlorambucil (10.7 months; 95%CI: 5.6–13.6; $p = 0.0018$; Fig. 2A). The results of a sensitivity analysis using the per-protocol set supported the primary analysis (Table 2 and Fig. 2B).

Progression-free survival

In the ITT population, endpoint events (progression or death) was observed in 42 (59.2%) patients in the BEN group compared with 65 (89.0%) patients in the CLB group. On the basis of endpoint events, median progression-free survival was 16.5 months (95%CI: 11.3–24.7) in the BEN group, that was significantly longer than 9.6 months (95%CI: 8.7–11.8) of the CLB group ($p < 0.001$, Fig. 3A). Sensitivity analysis on per-protocol set got similar results (Fig. 3B).

Overall Survival

In the ITT population, 16 deaths had occurred in the BEN group and 15 in the CLB group. Median overall survival

Table 1 Baseline Characteristics of the subjects

Characteristics	BEN (n = 71)	CLB (n = 73)
Age, years		
Mean (SD)	59.0 (9.42)	59.9 (9.45)
Median (min, max)	59.0 (31, 83)	59.0 (40, 78)
Age group, years-no (%)		
≥ 65	17 (23.9)	21 (28.8)
< 65	54 (76.1)	52 (71.2)
Sex-no (%)		
Female	21 (29.6)	15 (20.5)
Male	50 (70.4)	58 (79.5)
ECOG performance status -no (%)		
0	31 (43.7)	27 (37.0)
1	32 (45.1)	38 (52.1)
2	8 (11.3)	8 (11.0)
Binet stage-no (%)		
B	28 (39.4)	34 (46.6)
C	43 (60.6)	39 (53.4)
Rai stage-no (%)		
I	6 (8.5)	10 (13.7)
II	20 (28.2)	22 (30.1)
III	13 (18.3)	12 (16.4)
IV	32 (45.1)	29 (39.7)
Hemoglobin < 100 g/L-no (%)	23 (32.4)	19 (26.0)
Platelet < 100×10^9/L-no (%)	33 (46.5)	31 (42.5)
Lymph node size ≥ 5 cm-no (%)	19 (26.8)	16 (21.9)
Systemic symptom	47 (66.2)	53 (72.6)
B lymphocyte count ($\times 10^9$/L)	55.9 (72.2)	57.3 (70.8)
Comorbidities-no (%)		
Hypertension	10 (14.1)	13 (17.8)
Diabetes	5 (7.0)	10 (14.0)
Hepatitis	3 (4.2)	6 (8.2)

BEN bendamustine hydrochloride injection, *CLB* chlorambucil, *SD* standard deviation, *Min* minimum, *Max* maximum

Data were expressed as mean (SD), median or n (%)

Table 2 Tumor Response in full analysis population and per-protocol population

Variable	FAS		PPS*	
	BEN (N = 71)	CLB (N = 73)	BEN (N = 55)	CLB (N = 64)
objective response†				
No. of patients	49	27	44	27
% of patients (95% CI)‡	69.0 (56.9–79.5)	37.0 (26.0–49.1)	80.0 (67.0–89.6)	42.2 (29.9–55.2)
Difference vs. CLB-% points (95% CI)§	32.0 (16.6–47.5)	-	37.8 (21.8–53.9)	-
Best overall response-no. (%)				
Complete response	20 (28.2)	3 (4.1)	18 (32.7)	3 (4.7)
Partial response	29 (40.8)	24 (32.9)	26 (47.3)	24 (37.5)
Stable disease	10 (14.1)	39 (53.4)	9 (16.4)	36 (56.3)
Progressive disease	1 (1.4)	1 (1.4)	1 (1.8)	-
Could not be determined	11 (15.5)	6 (8.2)	1 (1.8)	1 (1.6)

BEN bendamustine hydrochloride injection, *CLB*, chlorambucil, *FAS* full analysis set, *PPS* per-protocol set, *CI* confidence interval

*PPS was used in a sensitivity analysis confirming robustness of the data

†Objective response (primary efficacy endpoint) was assessed according to 2008 iwCLL criteria by blinded independent central review

‡The 95% confidence interval is based on the Clopper–Pearson method

§The unweighted difference in objective response rates between the treatment groups was determined by the method of Newcombe

was not reached in either group. In the BEN group, 88% of patients were alive at 18 months and in the CLB group, 85% of patients were alive (Fig. 4A). There was no significant difference in the overall survival between two groups. The sensitivity analysis on per-protocol set exhibited consistent result (Fig. 4B).

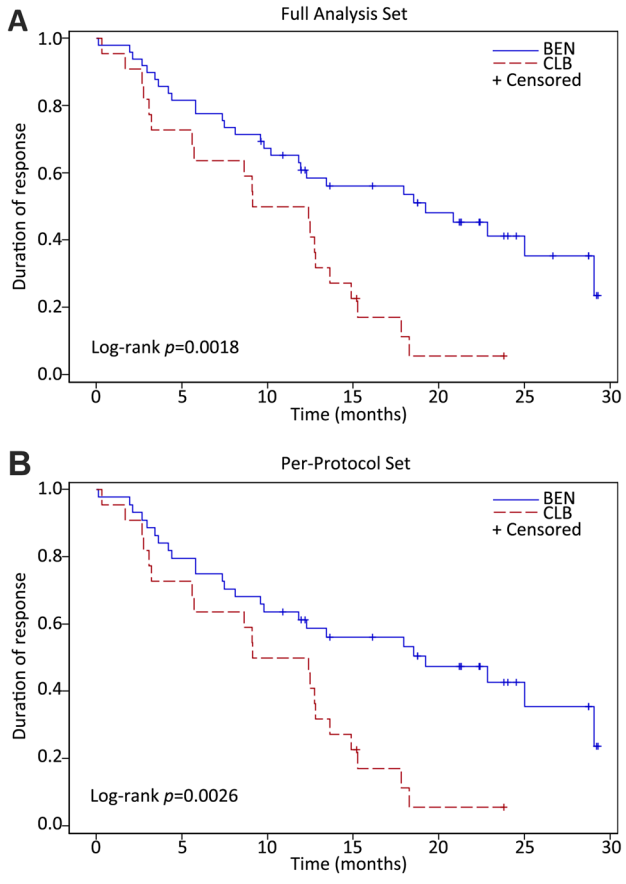

Fig. 2 Kaplan–Meier curves of duration of response in full analysis set (**A**) and per-protocol set (**B**)

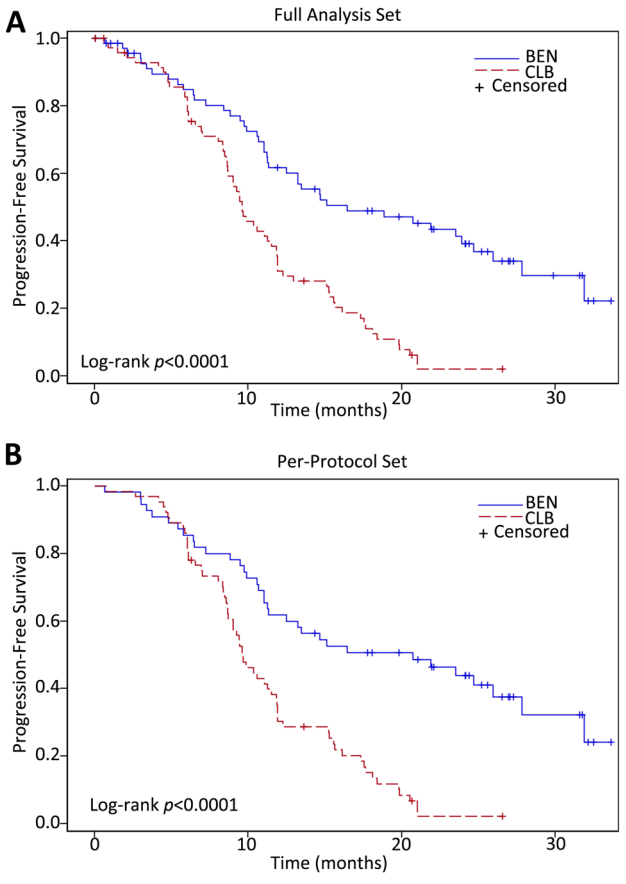

Fig. 3 Kaplan–Meier curves of progression-free survival in full analysis set (**A**) and per-protocol set (**B**)

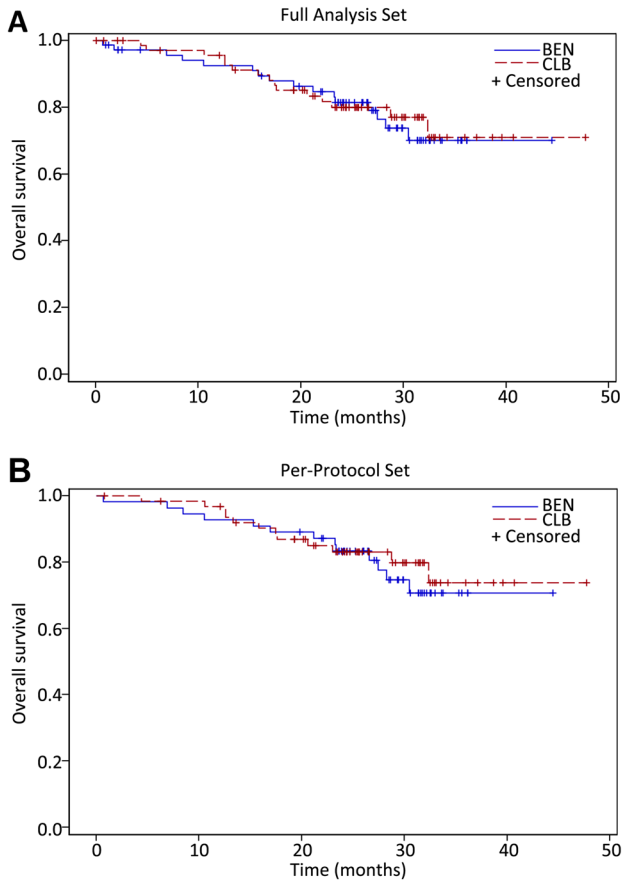

Fig. 4 Kaplan–Meier curves of overall survival in full analysis set (**A**) and per-protocol set (**B**)

Subgroup analysis

The benefit of bendamustine over chlorambucil was broadly consistent within subgroups, including patients with Binet stage B and those with Binet stage C (Table 3). For the patients with Binet stage B CLL in the ITT populatuion, the objective response rate was 75.0% (95%CI: 55.1–89.3) in the BEN group and 32.4% (95%CI: 17.4–50.5) in the CLB group ($p = 0.001$), with a difference rate of 42.7% (95%CI: 20.2–65.1). For the patients with Binet stage C CLL, objective response rate in BEN and CLB group were 65.1% (95%CI: 49.1–79.0) and 41.0% (95%CI: 25.6–57.0) respectively, with a difference rate of 24.1% (95%CI: 3.1–45.1; $p = 0.045$). Sensitivity analysis on per-protocol set confirmed the robustness of the data (Table 3).

Safety

The incidence of AEs were summarized in Table 4. Overall, AEs of any cause and regardless of attribution to treatmen were reported in 71 (100%) patients in the BEN group and 65 (89.0%) patients in the CLB group. These events were of grade 3 or higher in 81.7% and 32.9% of the patients, respectively. Events leading to discontinuation occurred in 28.2% of the patients in the BEN group and in 6.8% of those in the CLB group. Additionally, dose reduction of all trial drugs because of AEs were occurred in 37 (52.1%) and 4 (5.5%) patients, respectively. 15 (21.1%) patients in the BEN group experienced SAEs and one (1.4%) patient in the CLB group. Among them, SAEs suspected to be drug-related were recorded in 10 (14.1%) patients in the BEN group. Death due to AEs occurred in 3 (4.2%) and 1 (1.4%) of patients in two groups, respectively.

In the two groups, the most common hematologic AEs were neutropenia, thrombocytopenia, leukopenia, anemia, and lymphopenia. Neutropenia (78.9% vs. 50.7%), leukopenia (76.1% vs. 12.3%), and lymphopenia (43.2% vs. 2.7%) occurred more frequently in the BEN group than in the CLB group. The AEs of grade 3 or higher that was more frequent in the BEN group was neutropenia (49.3% and 17.8%), amd leukopenia (32.4% and 1.4%). Another AE of grade 3 or higher that were reported in at least 10% of the patients in two groups was thrombocytopenia (19.7% and 21.9%). The only grade 3 or higher AEs that was more frequent in the BEN group was lymphopenia (22.5%). The incidence of hyperglycemia (9.9% vs. 19.2%) and hyperbilirubinemia (12.7% vs. 13.7%) was lower in the BEN group than that in the CLB group. With regard to the non-hematologic AEs, nausea, vomit, fever, fatigue and rash occurred in at least 10% of the patients and more frequent in the BEN group.

Discussion

Although novel agents changed the treatment landscape of CLL dramatically in the last few years, the duration of drug exposure, the risks of toxic effects and resistance, as well as treatment costs are a great challenge for their extensive clinical application. Chemoimmunotherapy still has a role in the standard frontline therapy for a specific population [12]. Here, we present the results of the first randomized comparison of bendamustine versus chlorambucil for unfit Chinese patients with Binet stage B/C CLL. The results demonstrated the advantages of bendamustine in inducing the disease remissions, with higher proportions of patients achieving remission (69.01% vs. 36.99%) and complete remission (28.2% vs. 4.1%) compared with chlorambucil. Meanwhile, bendamustine resulted in significantly longer PFS and DR, which clearly favors the bendamustine treatment. Additionally, the present study reported a favorable and acceptable safety profile for bendamustine in Chinese patients with Binet stage B/C CLL. Overall, the data from this phase III trial suggest that bendamustine is an efficacious and safe agent in this population.

Table 3 Tumor Response in the subgroups stratified by Binet stage

Variable	Binet stage B		Binet stage C	
FAS population	BEN (N = 28)	CLB (N = 34)	BEN (N = 43)	CLB (N = 39)
objective response*				
No. of patients	21	11	28	16
% of patients (95% CI)†	75.0 (55.1–89.3)	32.4 (17.4–50.5)	65.1 (49.1–79.0)	41.0 (25.6–57.0)
Difference vs. CLB-% points (95% CI)‡	42.7 (20.2–65.1)	-	24.1 (3.1–45.1)	-
Best overall response-no. (%)				
Complete response	9 (32.1)	2 (5.9)	11 (25.6)	1 (2.6)
Partial response	12 (42.9)	9 (26.5)	17 (39.6)	15 (38.5)
Stable disease	4 (14.3)	20 (58.8)	6 (14.0)	19 (48.7)
Progressive disease	-	1 (2.9)	1 (2.3)	-
Could not be determined	3 (10.7)	2 (5.9)	8 (18.6)	4 (10.3)
PPS population§	BEN (N = 22)	CLB (N = 30)	BEN (N = 33)	CLB (N = 34)
objective response*				
No. of patients	19	11	25	16
% of patients (95% CI)†	86.4 (65.1–97.1)	36.7 (19.9–56.1)	75.8 (57.7–88.9)	47.0 (29.8–64.9)
Difference vs. CLB-% points (95% CI)‡	49.7 (27.3–72.1)	-	28.7 (6.4–51.0)	-
Best overall response-no. (%)				
Complete response	9 (40.9)	2 (6.7)	9 (27.3)	1 (2.6)
Partial response	10 (45.5)	9 (30.0)	16 (48.5)	15 (38.5)
Stable disease	3 (13.6)	18 (60.0)	6 (18.2)	18 (48.7)
Progressive disease	-	-	1 (3.0)	-
Could not be determined	-	1 (3.3)	1 (3.0)	-

BEN bendamustine hydrochloride injection, *CLB* chlorambucil, *FAS* full analysis set, *PPS* per-protocol set, *CI* confidence interval

*Objective response (primary efficacy endpoint) was assessed according to 2008 iwCLL criteria by blinded independent central review

†The 95% confidence interval is based on the Clopper–Pearson method

‡The unweighted difference in objective response rates between the treatment groups was determined by the method of Newcombe

§PPS was used in a sensitivity analysis confirming robustness of the data

In the present study, we noticed that the enrolled patients have a younger median age (59 years, range 31–83 years) compared with the average diagnosis age of ~ 70 years in Western countries [22]. Consistently, in several previous reports, the majority of Chinese patients with CLL generally had a young age of fewer than 65 years [15, 38]. It is likely that the development of CLL depends on the interplay of a genetic predisposition with exposure to environmental factors [22]. Thus, genetic disparities, eating habits, or environmental factors may account for the ethnic difference in diagnosis age. Besides, the proportion of younger patients with CLL seems to increase due to more frequent blood testing [11]. This reinforces the necessity for the investigation on the efficacy and safety of bendamustine in the Chinese population.

Bendamustine was associated with a higher objective response rate and complete response rate than the chlorambucil. This finding was consistent with the results of the previous trial in Caucasia patients [13]. The higher complete response rate achieved with bendamustine is an important finding because there is evidence that the higher complete response rate is associated with longer progression-free survival, which is then beneficial to improved quality of life [7, 32]. In our study, the mean progression-free survival in bendamustine-treated patients was nearly two-fold compared with chlorambucil-treated patients (16.5 months vs 9.6 months), supporting this opinion. Meanwhile, bendamustine induced more durable remissions compared with chlorambucil (19.2 months vs. 10.7 months) in this population. The bendamustine-induced duration of response was comparable with approximately 21 months of bendamustine monotherapy reported in Caucasia patients [14]. Meanwhile, the 19.2 months duration of response induced with bendamustine is higher than the estimated 8.7 months recently reported in Japanese [20]. These promising results highlight the favorable benefit of bendamustine in the Chinese population. However, median overall survival was not reached in both groups and then no difference was observed at the time of data cutoff, although patients showing any response had longer survival than non-responders. It is most probably because of the very small number of death events that occurred. Similar to the previous study in Caucasia patients,

Table 4 Adverse events of any cause in safety population

Event, no. of patients (%)	BEN (n = 71)		CLB (n = 73)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Any events	71 (100.0)	58 (81.7)	68 (93.2)	24 (32.9)
Any event leading to discontinuation	20 (28.2)	18 (25.4)	5 (6.8)	4 (5.5)
Any significant events*	44 (62.0)	38 (53.5)	9 (12.3)	8 (11.0)
Any adverse reactions†	70 (98.6)	53 (74.6)	66 (90.4)	22 (30.1)
Event occurring in ≥ 10% of patients in either group				
Neutropenia	56 (78.9)	35 (49.3)	37 (50.7)	13 (17.8)
Thrombocytopenia	42 (59.2)	14 (19.7)	44 (60.3)	16 (21.9)
Leukopenia	54 (76.1)	23 (32.4)	9 (12.3)	1 (1.4)
Anemia	28 (39.4)	0 (0.0)	16 (21.9)	1 (1.4)
Lymphopenia	33 (46.5)	21 (29.6)	2 (2.7)	0 (0.0)
Hyperglycemia	7 (9.9)	2 (2.8)	14 (19.2)	1 (1.4)
Hyperbilirubinemia	9 (12.7)	0 (0.0)	10 (13.7)	1 (1.4)
Hypoproteinemia	8 (11.3)	0 (0.0)	2 (2.7)	0 (0.0)
Elevated lactate dehydrogenase	10 (14.1)	0 (0.0)	9 (12.3)	0 (0.0)
Elevated alanine aminotransferase	17 (23.9)	1 (1.4)	5 (6.8)	0 (0.0)
Elevated aspartate aminotransferase	15 (21.1)	1 (1.4)	6 (8.2)	0 (0.0)
Nausea	34 (47.9)	1 (1.4)	5 (6.8)	0 (0.0)
Vomit	20 (28.2)	2 (2.8)	5 (6.8)	1 (1.4)
Anorexia	16 (22.5)	1 (1.4)	1 (1.4)	0 (0.0)
Fever	23 (32.4)	1 (1.4)	6 (8.2)	1 (1.4)
Fatigue	12 (16.9)	3 (4.2)	7 (9.6)	0 (0.0)
Rash	21 (29.6)	1 (1.4)	1 (1.4)	0 (0.0)

BEN bendamustine hydrochloride injection, *CLB* chlorambucil

*Significant events were defined as events that led to dose reduction, interruption, or discontinuation, other than a serious events

†Adverse reactions were defined as AEs that classified as definitely or possibly related to investigational drugs

the benefit of bendamustine over chlorambucil was broadly consistent in different Binet stages [13]. However, despite bendamustine monotherapy induced better responses clinically, the use of chemoimmunotherapy, including bendamustine and chlorambucil, is steadily declining [4]. In recent years, a number of highly active novel agents, including kinase inhibitors (e.g. ibrutinib, acalabrutinib), an antagonist of BCL-2 (e.g. venetoclax), and new anti-CD20 monoclonal antibodies (e.g. rituximab, obinutuzumab), have been added to the therapeutic armamentarium for CLL [5]. The accumulative data support the widespread use of bendamustine plus rituximab (i.e. BR regimen) in CLL treatment since it can increase the objective response rate (88%) and progression-free survival (33.9 months) compared with the bendamustine monotherapy [9]. More importantly, the BR regimen is associated with a lower risk for myelosuppression [8]. Although chlorambucil plus rituximab (R-Clb), or bendamustine plus ofatumumab or obinutuzumab have been compared with BR regimen [17, 29], to data, there is no evidence that these regimens are superior to BR in CLL. In general, the bendamustine monotherapy or BR regimen may offer a better risk–benefit ratio [28], providing direct evidence for the bendamustine in the Chinese population.

In light of the safety analysis, the present study demonstrated an acceptable safety profile for bendamustine in Chinese patients with CLL. The safety profiles of bendamustine and chlorambucil in the present study were generally consistent with the known profiles, as previously reported in other studies [13, 18]. There were no new safety signals identified in the Chinese population. Myelosuppression, including grade 3/4 neutropenia (49.3% and 17.8%) and thrombocytopenia (19.7% and 21.9%) was the primary AEs associated with both bendamustine and chlorambucil. In addition, leukopenia (32.4%) and lymphopenia (29.6%) are other frequent AEs of grade 3/4 caused by bendamustine, while not by chlorambucil. Even so, the majority of AEs were manageable and tolerable, which resolved soon with supportive care and dose reductions. Except for these above hematological toxicities, only a few patients who were treated with bendamustine and chlorambucil experienced grade 3 or higher AEs, such as hyperglycemia, vomit, fever, and fatigue. Notably, severe infections are also an important

safety concern of particular interest because they are a major cause of morbidity and mortality in CLL patients [1]. In the present study, grade 3/4 infections occurred in 11% of patients with bendamustine and none with chlorambucil; more importantly, no patient died due to infectious complications. The incidence of severe infections was generally comparable with the results from similar studies [13, 21]. However, severe infections rates of 11.4% and infection-related death of 14% have been recently reported for BTK inhibitor ibrutinib [31]. Meanwhile, the combination therapy (e.g. FCR and BR) reported the more frequent severe infections (39.8% and 25.4%) in similar populations [8]. Moreover, the safety profile of bendamustine was similar to the results from a single-arm trial in the Chinese population with NKL [26]. Overall, bendamustine is safe in the Chinese population, without new unexpected safety signals.

Although this was a randomized, controlled trial, several limitations exist. Firstly, the investigational drug (bendamustine) and comparator (chlorambucil) are no longer the standard frontline treatments for the majority of CLL patients, especially for young patients. Nevertheless, evidence gaps in the Chinese population are still worth filling, and meanwhile, these low-intensity drugs remain appropriate for first-line therapy in physically unfit patients. Secondly, the findings of this study are limited by the fact that it was not a double-blind design, but rather, was an open-label study, which might lead to the subconscious bias favorable to the experimental group. However, the results have been assessed by the independent review committee. This aspect ensures the quality of this study. In addition, the present study had a relatively small sample size. Even so, it has sufficient statistical power to reach the intended target for the primary endpoint. On the basis of the findings in this study, the large-scale trials on combination therapy with bendamustine or other agents are in progress or planned.

In conclusion, the results of this trial showed that bendamustine resulted in a significantly higher response rate and longer progression-free survival than chlorambucil in previously untreated Chinese patients with Binet stage B/C CLL. The clinical benefit for bendamustine was observed across all categories of the Binet stage. Overall, these results validate the role of bendamustine as an effective first-line therapy in this Chinese population with a manageable toxicity profile.

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Authors' contribution DZ and WX conceptualized and designed the study. HM and CZ constructed the forms to be filled with patient data. DZ, WX, YH, YZ and DW performed the data extraction from multiple centers. XZ, YH, JY, CW, FM, JJ, XZ, KY, JH, and YL recruited samples and collected clinicalpathologic data from their respective centers. DZ and WX drafted the manuscript. All authors reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

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Data availability The datasets generated for this study are available on request to the corresponding author.

Declarations

Ethics approval The studies involving human participants were reviewed and approved by an institutional review board (Approval number: 2008[27] and 2008[71]-2). Written informed consent for participation was obtained from each patient.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Al-Sawaf O, Zhang C, Robrecht S, Fink A-M, Cramer P, Herling CD, Von Tresckow J, Lange E, Böttcher S, Kiehl MG et al (2020) Severe Infections in Patients with Chronic Lymphocytic Leukemia Treated with (Immuno-)Chemotherapy: A Pooled Analysis of Gcllsg Trials. Blood 136:18–19. https://doi.org/10.1182/blood-2020-139242
2. Bergmann MA, Goebeler ME, Herold M, Emmerich B, Wilhelm M, Ruelfs C, Boening L, Hallek MJ, German CLLSG (2005) Efficacy of bendamustine in patients with relapsed or refractory chronic lymphocytic leukemia: results of a phase I/II study of the German CLL Study Group. Haematologica 90:1357–1364. https://doi.org/10.3324/%25x
3. Bogeljić Patekar M, Milunović V, Mišura Jakobac K, Perica D, Mandac Rogulj I, Kursar M, Planinc-Peraica A, Ostojić Kolonić S (2018) Bendamustine: an Old Drug in the New Era for Patients with Non-Hodgkin Lymphomas and Chronic Lymphocytic Leukemia. Acta Clin Croat 57:542–553. https://doi.org/10.20471/acc.2018.57.03.18
4. Burger JA (2020) Treatment of Chronic Lymphocytic Leukemia. N Engl J Med 383:460–473. https://doi.org/10.1056/NEJMra1908213
5. Burger JA, O'Brien S (2018) Evolution of CLL treatment - from chemoimmunotherapy to targeted and individualized therapy. Nat Rev Clin Oncol 15:510–527. https://doi.org/10.1038/s41571-018-0037-8
6. Call TG, Norman AD, Hanson CA, Achenbach SJ, Kay NE, Zent CS, Ding W, Cerhan JR, Rabe KG, Vachon CM (2014) Incidence of chronic lymphocytic leukemia and high-count monoclonal B-cell lymphocytosis using the 2008 guidelines. Cancer 120:2000–2005. https://doi.org/10.1002/cncr.28690
7. Eichhorst B, Al-Sawaf O, Hallek M (2019) Initial therapy of chronic lymphocytic leukemia. In: Hallek M, Eichhorst B, Catovsky D (eds) Chronic Lymphocytic Leukemia. Springer International Publishing, Cham, pp 79–96
8. Eichhorst B, Fink AM, Busch R, Kovacs G, Maurer C, Lange E, Köppler H, Kiehl MG, Soekler M, Schlag R et al (2014) Frontline Chemoimmunotherapy with Fludarabine (F), Cyclophosphamide (C), and Rituximab (R) (FCR) Shows Superior Efficacy in Comparison to Bendamustine (B) and Rituximab (BR) in Previously Untreated and Physically Fit Patients (pts) with Advanced Chronic Lymphocytic Leukemia (CLL): Final Analysis of an International, Randomized Study of the German CLL Study Group (GCLLSG)

(CLL10 Study). Blood 124:19–19. https://doi.org/10.1182/blood.V124.21.19.19
9. Fischer K, Cramer P, Busch R, Böttcher S, Bahlo J, Schubert J, Pflüger KH, Schott S, Goede V, Isfort S et al (2012) Bendamustine in combination with rituximab for previously untreated patients with chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol 30:3209–3216. https://doi.org/10.1200/jco.2011.39.2688
10. Goldin LR, Slager SL (2007) Familial CLL: genes and environment. Hematology Am Soc Hematol Educ Program 2007:339–345. https://doi.org/10.1182/asheducation-2007.1.339
11. Hallek M (2017) Chronic lymphocytic leukemia: 2017 update on diagnosis, risk stratification, and treatment. Am J Hematol 92:946–965. https://doi.org/10.1002/ajh.24826
12. Jain N (2018) Selecting Frontline Therapy for CLL in 2018. Hematology Am Soc Hematol Educ Program 2018:242–247. https://doi.org/10.1182/asheducation-2018.1.242
13. Knauf WU, Lissichkov T, Aldaoud A, Liberati A, Loscertales J, Herbrecht R, Juliusson G, Postner G, Gercheva L, Goranov S et al (2009) Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia. J Clin Oncol 27:4378–4384. https://doi.org/10.1200/JCO.2008.20.8389
14. Knauf WU, Lissitchkov T, Aldaoud A, Liberati AM, Loscertales J, Herbrecht R, Juliusson G, Postner G, Gercheva L, Goranov S et al (2012) Bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukaemia: updated results of a randomized phase III trial. Br J Haematol 159:67–77. https://doi.org/10.1111/bjh.12000
15. Lan Q, Au WY, Chanock S, Tse J, Wong KF, Shen M, Siu LP, Yuenger J, Yeager M, Hosgood HD 3rd et al (2010) Genetic susceptibility for chronic lymphocytic leukemia among Chinese in Hong Kong. Eur J Haematol 85:492–495. https://doi.org/10.1111/j.1600-0609.2010.01518.x
16. Laurenti L, Efremov DG (2020) Therapeutic Targets in Chronic Lymphocytic Leukemia. Cancers 12:3259. https://doi.org/10.3390/cancers12113259
17. Leblond V, Laribi K, Ilhan O, Aktan M, Unal A, Rassam SMB, Schuh A, Widenius T, Johansson P, Raposo J et al (2012) Rituximab in Combination with Bendamustine or Chlorambucil for Treating Patients with Chronic Lymphocytic Leukemia: Interim Results of a Phase IIIb Study (MaBLe). Blood 120:2744–2744. https://doi.org/10.1182/blood.V120.21.2744.2744
18. Merkle K, Dittrich C, Juliusson G, Loscertales J, Liberati AM, Herbrecht R, Aldaoud A, Lissichkov T, Knauf WU (2007) Bendamustine Versus Chlorambucil in Treatment-Naive Patients with B-Cell Chronic Lymphocytic Leukemia (B-CLL): Results of an International Phase III Study. Blood 110:2043–2043. https://doi.org/10.1182/blood.V110.11.2043.2043
19. Michallet AS, Aktan M, Hiddemann W, Ilhan O, Johansson P, Laribi K, Meddeb B, Moreno C, Raposo J, Schuh A et al (2018) Rituximab plus bendamustine or chlorambucil for chronic lymphocytic leukemia: primary analysis of the randomized, open-label MABLE study. Haematologica 103:698–706. https://doi.org/10.3324/haematol.2017.170480
20. Ogawa Y, Izutsu K, Kiguchi T, Choi I, Takatsuka Y, Ando K, Suzumiya J (2017) A multicenter, single-arm, Phase II clinical trial of bendamustine monotherapy in patients with chronic lymphocytic leukemia in Japan. Int J Hematol 105:631–637. https://doi.org/10.1007/s12185-016-2178-9
21. Ohmachi K, Ando K, Ogura M, Uchida T, Itoh K, Kubota N, Ishizawa K, Yamamoto J, Watanabe T, Uike N et al (2010) Multicenter phase II study of bendamustine for relapsed or refractory indolent B-cell non-Hodgkin lymphoma and mantle cell lymphoma. Cancer Sci 101:2059–2064. https://doi.org/10.1111/j.1349-7006.2010.01635.x
22. Ruchlemer R, Polliack A (2013) Geography, ethnicity and "roots" in chronic lymphocytic leukemia. Leuk Lymphoma 54:1142–1150. https://doi.org/10.3109/10428194.2012.740670
23. Shanafelt T (2013) Treatment of older patients with chronic lymphocytic leukemia: key questions and current answers. Hematology Am Soc Hematol Educ Program 2013:158–167. https://doi.org/10.1182/asheducation-2013.1.158
24. Shanafelt TD, Wang V, Kay NE, Hanson CA, O'Brien SM, Barrientos JC, Erba HP, Stone RM, Litzow MR, Tallman MS (2018) A Randomized Phase III Study of Ibrutinib (PCI-32765)-Based Therapy Vs. Standard Fludarabine, Cyclophosphamide, and Rituximab (FCR) Chemoimmunotherapy in Untreated Younger Patients with Chronic Lymphocytic Leukemia (CLL): A Trial of the ECOG-ACRIN Cancer Research Group (E1912). Blood 132:LBA-4-LBA-4. https://doi.org/10.1182/blood-2018-120779
25. Shanafelt TD, Wang XV, Kay NE, Hanson CA, O'Brien S, Barrientos J, Jelinek DF, Braggio E, Leis JF, Zhang CC et al (2019) Ibrutinib-Rituximab or Chemoimmunotherapy for Chronic Lymphocytic Leukemia. N Engl J Med 381:432–443. https://doi.org/10.1056/NEJMoa1817073
26. Shi YK, Hong XN, Yang JL, Xu W, Huang HQ, Xiao XB, Zhu J, Zhou DB, Han XH, Wu JQ et al (2021) Bendamustine treatment of Chinese patients with relapsed indolent non-Hodgkin lymphoma: a multicenter, open-label, single-arm, phase 3 study. Chin Med J (Engl) 134:1299–1309. https://doi.org/10.1097/CM9.0000000000001463
27. Skånland SS, Mato AR (2021) Overcoming resistance to targeted therapies in chronic lymphocytic leukemia. Blood Adv 5:334–343. https://doi.org/10.1182/bloodadvances.2020003423
28. Stauder R, Eichhorst B, Hamaker ME, Kaplanov K, Morrison VA, Osterborg A, Poddubnaya I, Woyach JA, Shanafelt T, Smolej L et al (2017) Management of chronic lymphocytic leukemia (CLL) in the elderly: a position paper from an international Society of Geriatric Oncology (SIOG) Task Force. Ann Oncol 28:218–227. https://doi.org/10.1093/annonc/mdw547
29. Stilgenbauer S, Leblond V, Foà R, Böttcher S, Ilhan O, Knauf W, Mikuskova E, Renner C, Tausch E, Woszczyk D et al (2018) Obinutuzumab plus bendamustine in previously untreated patients with CLL: a subgroup analysis of the GREEN study. Leukemia 32:1778–1786. https://doi.org/10.1038/s41375-018-0146-5
30. Van den Broek E, Kater A, Van de Schans S, Karim-Kos H, Janssen-Heijnen M, Peters W, Nooijen P, Coebergh J, Posthuma E (2012) Chronic lymphocytic leukaemia in the Netherlands: trends in incidence, treatment and survival, 1989–2008. Eur J Cancer 48:889–895. https://doi.org/10.1016/j.ejca.2011.06.053
31. Varughese T, Taur Y, Cohen N, Palomba ML, Seo SK, Hohl TM, Redelman-Sidi G (2018) Serious Infections in Patients Receiving Ibrutinib for Treatment of Lymphoid Cancer. Clin Infect Dis 67:687–692. https://doi.org/10.1093/cid/ciy175
32. Woods B, Hawkins N, Dunlop W, O'Toole A, Bramham-Jones S (2012) Bendamustine versus chlorambucil for the first-line treatment of chronic lymphocytic leukemia in England and Wales: a cost-utility analysis. Value Health 15:759–770. https://doi.org/10.1016/j.jval.2012.03.1389
33. Woyach JA, Johnson AJ (2015) Targeted therapies in CLL: mechanisms of resistance and strategies for management. Blood 126:471–477. https://doi.org/10.1182/blood-2015-03-585075
34. Yang F, Kumar A, Rojanasarot S, Schommer J, Shao R (2018) Cost-Effectiveness of Ibrutinib and Rituximab for the Relapsed or Refractory Chronic Lymphocytic Leukemia in China. Value Health 21:S31
35. Yang SM, Li JY, Gale RP, Huang XJ (2015) The mystery of chronic lymphocytic leukemia (CLL): Why is it absent in Asians and what does this tell us about etiology, pathogenesis and biology? Blood Rev 29:205–213. https://doi.org/10.1016/j.blre.2014.12.001

36. Zhu J, Ma J, Union for China Lymphoma Investigators of Chinese Society of Clinical O (2021) Chinese Society of Clinical Oncology (CSCO) diagnosis and treatment guidelines for malignant lymphoma 2021 (English version). Chinese j cancer res = Chung-kuo yen cheng yen chiu 33:289–301. https://doi.org/10.21147/j.issn.1000-9604.2021.03.01
37. Zhu S, Tao L, Wang J, Du L, Xiao D, Zhang Y, Xuan J (2018) Disease Burden of Chemotherapy and Chemoimmunotherapy Treatment of Chronic Lymphocytic Leukemia (CLL) Patients in China. Value Health 21:S108. https://doi.org/10.1016/j.jval.2018.07.829
38. Zou YX, Tang HN, Zhang J, Tang XL, Qin SC, Xia Y, Zhu HY, Qiao C, Wang L, Fan L et al (2021) Low prevalence and independent prognostic role of del(11q) in Chinese patients with chronic lymphocytic leukemia. Transl Oncol 14:101176. https://doi.org/10.1016/j.tranon.2021.101176

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