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ORIGINAL ARTICLE

Patients' preferences for chronic lymphocytic leukemia treatment: The CHOICE study

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Abstract

Chronic lymphocytic leukemia (CLL) therapies differ in efficacy, side effects, route, frequency, and duration of administration. We assessed patient preferences for treatment attributes and evaluated associations with disease stage, treatment line, and socio-demographic characteristics in a cross sectional, observational study conducted at 16 Italian hematology centers. Study visits occurred between February

and July 2020; 401 adult patients with CLL (201 Watch and Wait (W&W), 200 treated) participated in a discrete choice experiment (DCE), composed of 8 choices between pairs of treatment profiles with different levels of 5 attributes of currently available CLL treatments (length of response, route and duration of administration, risk of side effects including diarrhea, infections, or organ damage). Health-related quality of life was assessed with the EQ-5D-5L, EORTC QLQ-C30 and QLQ CLL-16. Previously treated patients had longer disease duration (7 vs. 5 years), higher prevalence of serious comorbidities (45.5% vs. 36.2%) and high-risk molecular markers (unmutated IGHV 55.6% vs. 17.1%; TP53 mutation 15.2% vs. 4.0%). Health-related quality of life scores were similar between groups. In the DCE, W&W patients rated "possible occurrence of infections" highest (relative importance [RI] = 36.2%), followed by "treatment and relevant duration" (RI = 28.0%) and "progression-free survival (PFS)" (RI = 16.9%). Previously treated patients rated "treatment and relevant duration" highest (RI = 33.3%), followed by "possible occurrence of infections" (RI = 28.8%), "possible occurrence of organ damage" (RI = 19.4%), and "PFS" (RI = 9.8%). Concern over infection was rated highest overall; unexpectedly PFS was not among the most important criteria in either group, suggesting that the first COVID-19 pandemic wave may have influenced patient preferences and concerns about CLL therapy options.

KEYWORDS
chronic lymphocytic leukemia, discrete choice experiment, health-related quality of life, treatment preferences

1 | INTRODUCTION

Chronic lymphocytic leukemia (CLL), the most common leukemia among adults in Western countries (incidence about 4-5 per 100,000), primarily affects the older adult population (median age at diagnosis about 70 years), and has a higher prevalence in men.[1,2] CLL is a heterogeneous B lymphocyte condition that generally only requires treatment when symptomatic or progressive.[3,4] Progression involves the onset or worsening of lymphocytosis, adenopathy, hepatosplenomegaly, and bone marrow infiltration.[5,6] CLL causes dysregulation of innate and adaptive immunity,[7–9] which may be exacerbated by treatment[10,11]; infections are a common complication.[12] CLL may increase the risk of developing severe complications from COVID-19, in the prevaccine era.[13–15]

Newer targeted treatment options either block survival signaling through the B cell receptor, by inhibiting the Bruton tyrosine kinase or phosphatidylinositol 3-kinase delta (PI3Kδ), or interfere with the anti-apoptotic function of B cell leukemia/lymphoma 2.[4] These chemotherapy-free treatments have largely replaced chemo-immunotherapy (e.g., chlorambucil or fludarabine combined with an anti-CD20 agent) for CLL.[16] However, the development of these novel drugs has changed the CLL paradigm of therapy and complicated treatment choices. Recent guidelines recommend that treatment decisions should consider patient preferences, in addition to patient characteristics and the expected clinical course based on prognostic biomarkers.[4] Targeted therapies differ in terms of administration route and frequency, side effects and duration of therapy. These treatment attributes can influence patient preferences and play a key role in adherence to CLL treatment and in clinical outcomes, adherence being essential for successful treatment of chronic conditions,[17,18] including CLL.[19] Patient-reported health-related quality of life (HRQoL) and symptom burden also become critical aspects to consider when making treatment decisions.[20–22]

Discrete choice experiment (DCE) methodology is a widely used approach that allows the identification and evaluation of participants' treatment preferences and their importance in decision making.[23,24] It has rarely been used in the setting of CLL.[25–27]

The treatment options for CLL have undergone rapid evolution in recent years, to include also novel oral chemoimmunotherapy-free agents, some of which are administered continuously until progression, while others are administered as time-limited therapy involving fixed duration administration followed by a treatment-free period. Considering this new scenario in rapid evolution, with different alternative options now available in addition to conventional chemo-immunotherapy agents, we have conducted this study to assess HRQoL and preference for representative CLL treatment profiles among Watch and Wait (W&W) and treatment-experienced patients in routine clinical practice.

2 | PATIENTS AND METHODS

2.1 | Study design

This cross sectional, observational study was conducted in 16 Italian hematological centers managing ≥200 CLL patients/year. W&W or treatment-experienced adult patients with a confirmed diagnosis of CLL were eligible for enrollment; patients unable to take oral medications, those with a cognitive status that may impair questionnaire comprehension, and those receiving treatment for another malignancy were excluded. Participating sites obtained Local Ethics Committee approval before enrollment. Participants provided written informed consent to participation in the study and to treatment of their personal data in accordance with Italian law GDPR 679/2016.

2.2 | Description of the discrete choice experiment (DCE) methodology

Treatment attributes for CLL therapy were defined by a group of clinicians from hospitals managing ≥200 CLL patients/year. Attribute levels were based on a literature review of the available treatments and the opinions of clinicians. Treatment profiles included 5 attributes of currently available treatment options and associated levels: efficacy (in terms of length of response, progression-free survival (PFS)), route, frequency of administration and duration of therapy, and the likelihood of experiencing side effects (possible occurrence of infections, diarrhea, and organ damage) (Table 1). Treatment profiles presented to W&W and treated patients had different attribute levels for "treatment and relevant duration", "PFS" and "possible occurrence of diarrhea", to address differences in possible treatment patterns and related efficacy and side effects.

The attributes and levels were combined into 16 different treatment profiles for each cohort (treated and W&W), and these profiles were paired to yield 120 comparisons, from which representative comparisons satisfying the criteria of equilibrium and orthogonality recommended in the ISPOR DCE guidelines were selected,[24] finally resulting in a total of 80 different comparisons for W&W and 72 for treated patients. Each comparison listed two treatment profiles with the 5 above-mentioned attributes in one of each levels. Examples of DCE questionnaires were tested in a focus group of 18 W&W and treatment experienced CLL patients to assess the rate of comprehension and acceptance of the proposed attributes.

The 80 comparisons for W&W and 72 for treated patients were divided into blocks of 8 comparisons, each to be assigned to around 20 patients. To ensure balanced assignment of each block among participating centers and overall, the block (DCE questionnaire) was centrally assigned to any consecutive patient enrolled through the eCRF. Attributes and levels were explained to each patient at the study visit using the descriptions in Supplemental Table S1, and patients compiled the questionnaires through a specifically developed App (Supplemental Figure S1) on a dedicated tablet.

TABLE 1 Attributes and levels analyzed in the discrete choice experiment.

	Attribute levels	
Attribute	**W&W**	**Treated patients**
Treatment and relevant duration	□ Oral until progression	□ Oral until progression
	□ IV 6 months	□ IV 6 months
	□ Oral 6 months + IV 6 months	□ Oral 24 months + IV 6 months
	□ Oral 12 months + IV 6 months	□ Oral until progression + IV 6 months
Progression-free survival	□ 24 months	□ 18 months
	□ 36 months	□ 24 months
	□ 48 months	□ 60 months
	□ 60 months	
Possible occurrence of infections	□ 10%	□ 10%
	□ 15%	□ 15%
	□ 30%	□ 30%
Possible occurrence of diarrhea	□ 5%	□ 5%
	□ 10%	□ 15%
Possible occurrence of organ damage	□ 1%	□ 1%
	□ 6%	□ 6%
	□ 10%	□ 10%

2.3 | Socio-demographic, clinical and health-related quality of life (HRQoL) data collection

Patient socio-demographic, clinical and treatment data were collected by the physician as detailed in Supplemental Box S1.

Patients compiled the EORTC QLQ-C30,[28] the CLL-specific QLQ-CLL16 questionnaire (a more recent version, QLQ-CLL17, is currently available[29]) and the generic HRQoL instrument EQ-5D-5L.[30]

2.4 | Statistical analyses

The sample size based on $\alpha = 5\%$ resulted in $n = 192$ using established methods[31]; a recruitment target of 200 patients was set for each group to account for possible non completion of questionnaires. Study data were summarized using descriptive statistics. Health-related quality of life between-group differences were tested with *t*-test or Mann Whitney test, as appropriate. A *p*-value <0.05 was considered statistically significant.

The extent of preference for each level of an attribute was calculated by part-worth utility using a mixed logit model: a positive value indicates that an attribute level is preferred, the associated *p*-value indicates whether the part-worth utility value is significantly

different from 0. The relative importance [RI] of an attribute indicates its overall utility (calculated as the overall utility value for each attribute divided by the sum of overall utility values across all attributes). The mixed logit model calculated normalized mean preference weights (i.e., relative preference for each level with respect to the mean attribute effect). All levels were estimated as random parameters with a normal distribution. Adjusted analyses were made at the patient level by adding the covariates of age, sex, education, and disease duration.

Subgroup analyses evaluated differences in preference by adding interaction terms to the original mixed logit model. Main subgroups analyzed included age (<70 years vs. >70 years), employment status, comorbidity (Cumulative Illness Rating Scale, CIRS ≤7 vs. >7), geographic region (Northern, Central or Southern Italy). The effect of geographical location was explored to investigate the impact of the first COVID-19 pandemic wave on patient preferences, due to the higher impact of SARS-CoV-2 infections in the Northern regions during the study. All analyses were conducted with SAS 9.4 (SAS Institute, Inc.).

3 | RESULTS

Enrollment of 201 W&W and 200 treated patients with CLL took place from February to July 2020. The final evaluable population included 199 W&W and 198 treated patients.

The socio-demographic and clinical characteristics of both groups are presented in Table 2. The median value on the Cumulative Illness Rating Scale (CIRS) was 6 (IQR: 4–9)in both groups; 45.5% of the treated and 36.2% of the W&W patients had at least one body system involvement rated as serious/very serious (severe problem or constant disability/extremely severe problem requiring immediate treatment or severe functional impairment). Mean disease duration was longer in treated compared to W&W patients (8.2 vs. 6.6 years).

Among treated patients, 146 (73.7%) were on treatment at the visit; 61 (30.8%) were on their first line of treatment; 88/146 (60%) were receiving exclusively oral therapies, 65 ibrutinib and 23 venetoclax (Table 3).

At the study visit, most patients had RAI CLL stage 0 (36% in the treated and 39% in the W&W group), and Binet CLL stage A (44% in the treated and 65% in the W&W group) (Table 2). Most patients reported ≥1 major comorbidity (87.9% of treated and 88.9% of W&W patients). More patients in the treated group had high-risk genetic and molecular markers (del17p 14.1% vs. 2.5%, del11q 17.2% vs. 4.5%, mutated p53 15.2% vs. 4%, unmutated immunoglobulin variable heavy chain gene [IgVH] status 55.6% vs. 17.1%).

3.1 | Discrete choice analysis

Overall, respondents rated the "possible occurrence of infections" as the most important attribute, followed by "treatment and relevant duration". Descriptive data show how often each level of a profile was chosen (Supplemental Tables S2 and S3). W&W patients rated the "possible occurrence of infections" as the most important (RI = 36.2%), followed by "treatment and relevant duration" (RI = 28.0%), PFS (RI = 16.9%); "possible occurrence of organ damage" and "possible occurrence of diarrhea" seemed to have less impact on the decision, although it was still statistically significant. Among the different levels of each attribute, all were statistically different from each other except "oral treatment until progression" versus "oral 12 months + IV 6 months", and "60 months PFS" versus "48 months PFS" (Figure 1A, Supplementary Table S4). These results were confirmed when adjusted for age, sex, education, and disease duration (Figure 2A, Supplementary Table S5).

Treated patients gave more importance to "treatment and relevant duration" (RI = 33.3%) followed by "possible occurrence of infections" (RI = 28.8%). The RIs of the remaining attributes were lower, including "possible occurrence of organ damage", "PFS", and "possible occurrence of diarrhea". The levels of each attribute were statistically different from the first level for all attributes except PFS (Supplementary Table S6, Figure 1B). These results were confirmed when adjusted for age, sex, education, and disease duration (Supplementary Table S7, Figure 2B).

Relative importance of attributes in the DCE analysis for W&W and treated patients are summarized in Figure 3.

3.2 | Subgroup analyses of the discrete choice experiment

Stratifying W&W patients by age (<70 vs. >70 years), revealed a higher rating for "possible occurrence of organ damage" among younger W&W patients, whereas younger treated patients rated the "possibility of infections" higher than "treatment and relevant duration" and these preferences were inverted in older treated patients. Treated patients who were employed rated the "occurrence of infections" highest, while retired patients rated "treatment and relevant duration" highest. Treated patients with lower comorbidity (CIRS ≤7) rated the "possibility of infections" highest, while those with higher comorbidity rated "treatment and relevant duration" highest.

An exploratory subgroup analysis was conducted between patients from the Northern region, more impacted by the first wave of the pandemic, and the Central and Southern regions. W&W patients in the North (n = 83) rated "treatment and relevant duration" highest (RI = 40.3%), followed by the "possibility of infection" (RI = 27.2%), while W&W patients in the Central/Southern regions (n = 113) rated the "possibility of infections" highest (RI = 43.4%), similarly to the general study population, followed by the "possible occurrence of organ damage" (RI = 21.6%); results for treated patients were similar in all regions.

3.3 | Health-related quality of life

There were no statistically meaningful differences between W&W and treated groups on the EQ-5D-5L questionnaire, and most scales

TABLE 2 Socio-demographic characteristics by treatment history.

Characteristic	Treated (n = 198)	W&W (n = 199)
Age, median (IQR)	70.0 (61–76)	68.0 (61–75)
Sex, *n* (%)		
Female	63 (31.8)	77 (38.7)
Male	135 (68.2)	122 (61.3)
Smoking status, *N* (%)		
Current	19 (9.6%)	26 (13.1)
Former	47 (23.7)	33 (16.6)
Never	132 (66.7)	140 (70.4)
Education level completed, *n* (%)		
Below high school	134 (67.7)	127 (63.8)
High school	44 (22.2)	48 (24.1)
University	20 (10.1)	24 (12.1)
Employment		
Employed	58 (29.3)	68 (34.2)
Retired	131 (66.2)	118 (59.3)
Other	9 (4.5)	13 (6.5)
Civil status		
Married	160 (80.8)	152 (76.4)
Single/Widowed/Divorced	38 (19.2)	47 (23.6)
Geographic Region, *n*		
Northern Italy	94	83
Central/Southern Italy	104	113
CLL duration, mean ± SD years	8.2 ± 5.4	6.6 ± 5.7
Total CIRS score, median (IQR)	6.0 (4–9)	6.0 (4–8)
≥1 additional major pathology, *n* (%)	174 (87.9)	177 (88.9)
Obesity (BMI ≥30), *n* (%)	24 (12.1)	30 (15.6)
RAI stage, *n* (%)		
0	71 (35.9)	78 (39.2)
I	30 (15.2)	41 (20.6)
II	45 (22.7)	40 (20.1)
III	5 (2.5)	9 (4.5)
IV	22 (11.1)	12 (6.0)
NA	24 (12.1)	14 (7.0)
Missing	1 (0.5)	5 (2.5)
Binet stage, *n* (%)		
A	88 (44.4)	130 (65.3)
B	60 (30.3)	38 (19.1)
C	27 (13.6)	17 (8.5)
NA	22 (11.1)	13 (6.5)
Missing	1 (0.5)	1 (0.5)

Abbreviations: BMI, body mass index; CIRS, Cumulative Illness Rating Scale; CLL, chronic lymphocytic leukemia; NA, not available.

indicated limited or no impact. The median QoL score on a 100-point VAS (higher scores indicate higher QoL) was 75 for the treated group and 80 for the W&W group. Scores on the EORTC QLQ-C30 and the EORTC QLQ-CLL16 (CLL Module) were also similar between treated and W&W patients, suggesting that CLL treatment has a limited impact on QoL. There were marginal statistically significant differences favoring the W&W group for QLQ-C30 role functioning ($p = 0.024$) and social functioning ($p = 0.003$) (Supplemental Figure S2), and for the QLQ CLL-16 infection scale ($p < 0.001$, Supplemental Figure S3); however, these differences did not exceed thresholds for clinical significance.[32]

TABLE 3 Chronic lymphocytic leukemia treatment history and status in 198 treated patients.

Treatment	
Currently receiving treatment, *n* (%)	146 (73.7)
Currently in first line, *n* (%)	61 (30.8)
Current treatment, *n* (% of 146)	
Chemoimmunotherapy	12 (8.2)
Ibrutinib	65 (44.5)
Idelalisib + rituximab	6 (4.1)
Venetoclax + rituximab	16 (11.0)
Venetoclax	23 (15.8)
Other	24 (16.4)
Previous treatments	
≥1 treatment, *n* (%)	137 (69.2)
1–3 treatments, *n* (%)	121 (88.3)

4 | DISCUSSION

International CLL Guidelines indicate that treatment decisions should consider patient preferences.[4] Previous DCEs have explored patient preferences for CLL treatment attributes,[25,26,33] and factors that determine CLL treatment selection by clinicians[34]; however, recent evolution of the available treatment options necessitates a reappraisal.[25–27] This study employed a rigorous statistical design to collect data on patient preferences for CLL treatment attributes and provide valuable insight from centers distributed throughout Italy. Influence of the concurrent COVID-19 pandemic may be seen in the reduced weight given to long-term outcomes like PFS, unlike in previous studies,[25,26] probably reflecting concern over infections in patients with CLL, for whom the risk of infections can be increased by some treatments, and is normally considered a possible severe side effect. Concern over social distancing and travel may also have influenced the choice of a treatment that does not require regular clinical visits. The preference for oral treatments may also be due to familiarity with oral CLL treatments among patients in the treated cohort, 60% of whom were already receiving exclusively oral therapy. Among treated patients, the most influential factor was not "reduced infection risk", but a preference for oral treatment over IV, as identified in previous studies.[35,36]

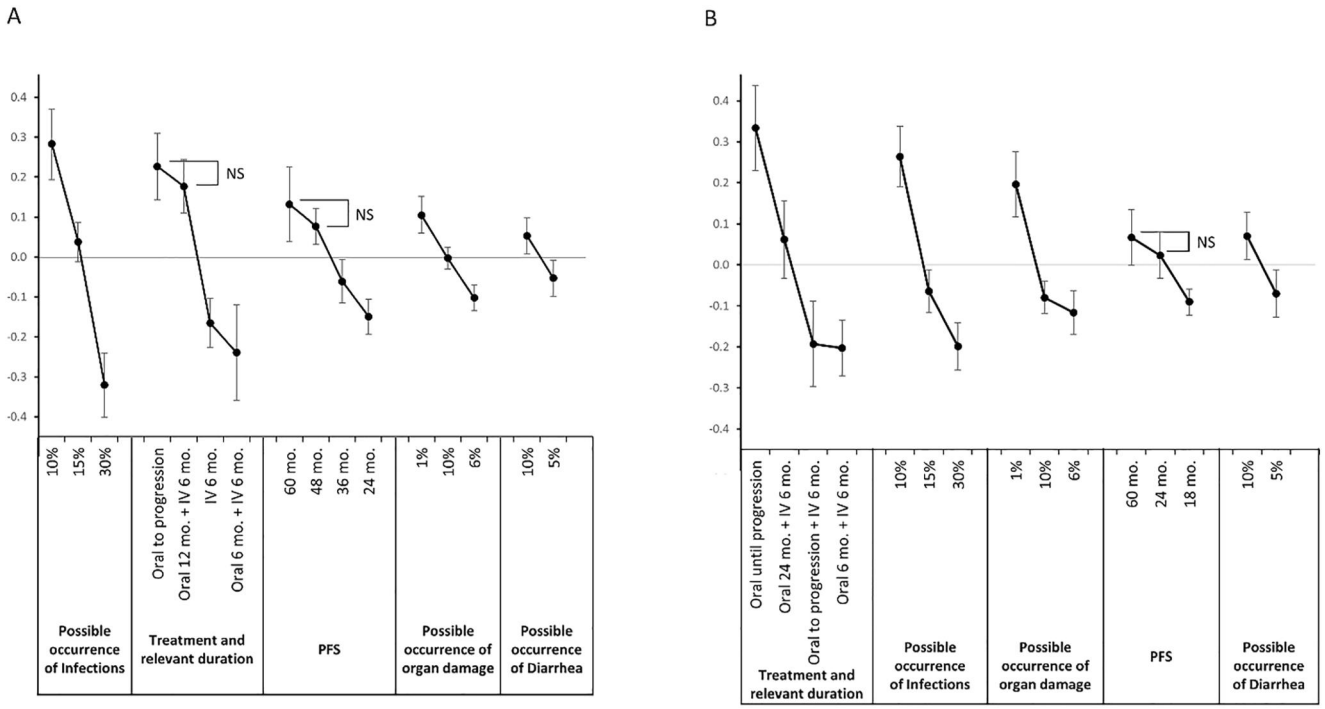

FIGURE 1 Part-worth utility values normalized to have a mean of 0 for each attribute level from the mixed logit model. (A) 198 W&W patients and (B) 199 treated patients, of which 146 (73.7%) were currently receiving treatment. Error bars represent 95% confidence intervals. Unless otherwise indicated with "NS", all differences between the first and subsequent levels for each attribute are significant.

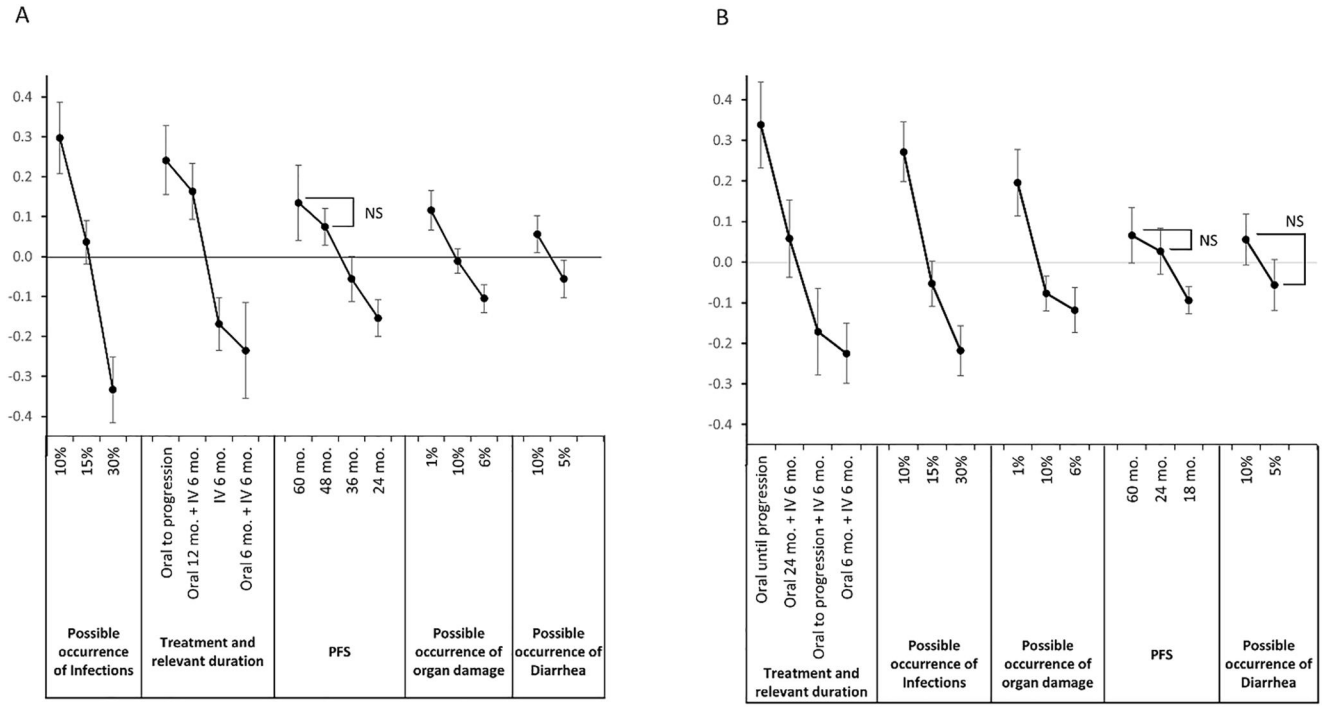

FIGURE 2 Part-worth utility values normalized to have a mean of 0 for each attribute level from the mixed logit model adjusted for age, sex, education, and disease duration. (A) 198 W&W patients and (B) 199 treated patients, of which 146 (73.7%) were currently receiving treatment. Error bars represent 95% confidence intervals. Unless otherwise indicated with "NS", all differences between the first and subsequent levels for each attribute are significant.

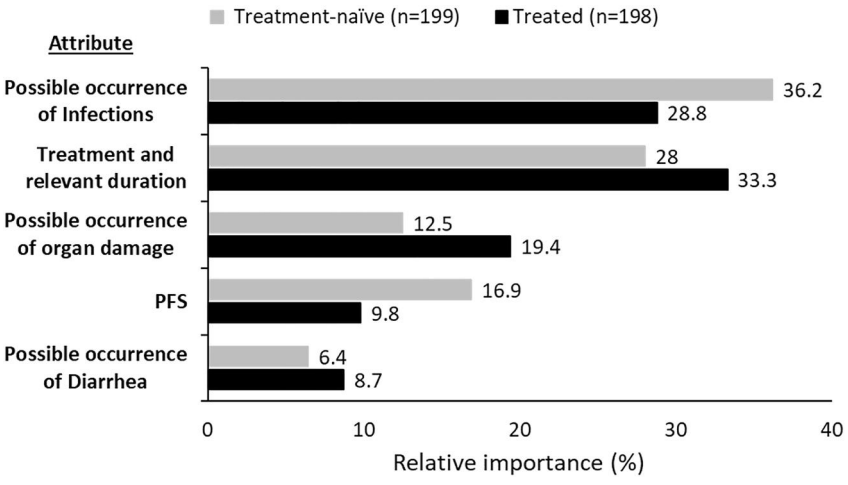

FIGURE 3 Relative importance (RI) of attributes in the discrete choice experiment analysis for W&W and treated patients. Calculated as the overall utility value for each attribute divided by the sum of overall utility values across all attributes.

Chronic lymphocytic leukemia is a chronic disease with a relatively indolent course, and a large proportion of diagnosed patients are not treated but undergo observation for signs of disease progression (i.e., "watchful waiting"). Since receiving a treatment for CLL might likely impact preferences for subsequent treatments, we collected data on a W&W cohort and a treatment-experienced cohort that included patients in the first line and relapsed/refractory settings. The high number of W&W CLL patients enrolled represents a strength of the study, as this population is scarcely represented in literature,[26] and we had the opportunity to explore potential differences in the cohorts related to having been exposed to an antileukemic treatment. In addition to recruiting a large representative study population, this DCE designed as a clinical study involved the administration of questionnaires during a clinical visit, with the support of medical personnel to clarify any doubts, and collected disease related data with a scientifically robust methodology.

Patient characteristics in the two cohorts reflected the indications for treatment, with more treated patients having high-risk biomarkers, longer disease duration and somewhat later-stage disease, validating the expected CLL patient profiles. Most of the treated patients (60%) had received or were receiving oral treatments, and only 8.2% were receiving chemoimmunotherapy, as expected from the current treatment landscape.

Few studies have assessed HRQoL in CLL patients in the real-world setting, and most of the data on this topic are from clinical trials.[37,38] In this large cross-sectional study with a range of CLL treatment status - from W&W to heavily treated patients - treated and W&W patients with CLL had similar QoL results. Consistent with previous reports, fatigue was perceived as having the most impact, and concern about future health was the most impaired domain of the QLQ CLL-16 (CLL module) questionnaire; however, none of the differences between groups can be considered of clinical importance according to recently established thresholds.[32]

In 2016, Landfeldt et al.[25] published the results from an online DCE that estimated preferences for CLL treatment attributes in a sample of 44 patients with CLL (14%), 72 clinicians with recent experience treating CLL (23%) and 200 members of the general population (63%) recruited from online panels in Germany or Sweden. Treatment attributes included "fatigue", "nausea", "overall survival", "progression-free survival", "risk of serious infections", and "treatment administration". In the whole study population, "overall survival" had the highest mean RI (36%), followed by "risk of serious infection" (21%). Among the subgroups, "overall survival" was more important to clinicians, while "treatment administration" was more important to patients. Concern over the "risk of serious infections" was higher in the general population than among clinicians. The relatively small number of patients enrolled ($n = 44$) may limit the generalizability of the result to the CLL patient population, and no subgroup analysis of treated versus W&W patients was performed.

In 2016, Mansfield et al.[26] conducted an online DCE that assessed preferences for the treatment attributes "chance of severe infection", "chance of organ damage", "diarrhea", "how long until the cancer advances", "how you take the medicine" in 384 US patients recruited from a CLL patient database.[26] Survey respondents placed the highest RI on longer PFS, followed by lower risk of severe infection. Subgroup analysis did not reveal differences in preferences among patients who were treatment-naïve, treated in first line, or treated for relapsing disease; however, W&W patients were underrepresented in this study ($n = 20$). Our results contrast the findings of Mansfield et al., not only in that our patients placed more importance on "treatment and relevant duration" (treated patients) or "possible occurrent of infections" (W&W patients) than on PFS, but also in revealing significant differences in preferences between W&W and treated patients.

More recently, Le et al. assessed preferences for first line CLL treatment attributes among 151 oncologists and 220 W&W patients using an online DCE.[27] Attributes included the "2-year PFS" rate, risks of 5 different adverse events (atrial fibrillation, infection, tumor lysis syndrome, bleeding, musculoskeletal pain), risk of treatment discontinuation due to AEs, and the duration and route of administration. Increasing PFS had the highest RI for both oncologists (30%) and patients (40%), whereas the risks of atrial fibrillation, infection, and discontinuation due to AEs were also important to both groups.

The main limitation of our study was its cross-sectional design, which does not allow us to evaluate changes in QoL with respect to the impact of the pandemic, or to the effects of treatment, if any. The CHOICE study was planned to understand CLL patients' preferences toward different treatment attributes, but the results have been impacted by the concurrent COVID-19 pandemic. The emphasis placed on possible infections in the CHOICE study, in contrast to previously published DCEs,[25,26] could be due to uncertainty during the first COVID-19 pandemic wave and the great attention that media had dedicated to the issue of infection in general, especially for vulnerable individuals such as patients with CLL. Limitations on hospital access during that period, as well as requirements for protective masks and social distancing might also have influenced patients' responses. The flood of information and misinformation may have influenced patients' perception of the risk associated with progression of a generally indolent condition like CLL and that of a viral infection that was proving rapidly fatal in a substantial proportion of people with similar characteristics.

5 | CONCLUSIONS

The CHOICE study provides insight into the attitude and beliefs of patients with CLL regarding the impact of the COVID-19 pandemic on health care for this category of patient, highlighting their preferences and concerns in a large cohort of CLL patients and allowing comparisons between treated and W&W patients. Our results indicate that pandemic restrictions and media focus on the danger of infections may have influenced not only the conduct of this study but also patients' perception of CLL and their future health, suggesting that patients may require more education and reassurance.

AUTHOR CONTRIBUTIONS

Paola Finsinger and Giuliana Gualberti were involved in the conception and organization of the study. Paolo Sportoletti, Luca Laurenti, Annalisa Chiarenza, Gianluca Gaidano, Elisa Albi, Francesca Romana Mauro, Livio Trentin, Daniele Vallisa, Fabrizio Pane, Antonio Cuneo, Francesco Albano, Giulia Zamprogna, Marta Coscia, Alessandro Gozzetti, and Gianluigi Reda were involved in the study execution and data collection. Paola Finsinger, Emilia Iannella, Simona Malgieri, Giuliana Gualberti, and Morena Caira participated in statistical analysis design and/or execution. All authors contributed to the preparation and critical review of the manuscript, and all of them approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from AbbVie srl. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the author(s) with the permission of AbbVie srl.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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