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What Are the Attributes Prioritized in the Choice of Therapy in Chronic Lymphocytic Leukemia? A Patient-physician Cross-matching Analysis of a Discrete Choice Experiment

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ABSTRACT

Several treatment options are available for chronic lymphocytic leukemia (CLL) and, for this reason, treatment choice can result challenging after introducing oral targeted agents. This study aims at comparing patients' and hematologists' preferences for attributes of CLL treatments. An online cross-sectional survey has been delivered to clinicians and patients affected by CLL in Italy. A discrete choice experiment has been conducted so to estimate each attribute's relative importance (RI) and assess the preference weight for each level of each attribute. An expert panel agreed on investigating the following attributes: progression-free survival (PFS) and measurable residual disease, route of administration/therapy duration and follow-up frequency, incidence of diarrhea (episodes/day), serious infections (grade 3 or 4), and atrial fibrillation. Overall, 746 patients and 109 clinicians accessed the survey, and 215 and 69, respectively, filled it in. The most important attributes were PFS (RI 30%) for hematologists and the risk of severe infections (RI 24%) for patients. Clinicians rated preference for maximum efficacy and lowest risk of severe infection very high (30%). Both patients and clinicians preferred oral administration while considering duration of therapy less relevant. The frequency of hospital appointments was negligible for patients, while clinicians preferred a quarterly frequency. Considering all attributes, diarrhea was weighted more by clinicians than by patients. Atrial fibrillation was not relevant for clinicians, while it was not negligible for patients. In conclusion, clinicians and patients favor an oral therapy, including continuous treatment, if associated with prolonged PFS, albeit with particular attention to the risk of serious infections.

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is the most common type of leukemia affecting adults in western countries, mainly affecting older adults, with a median age at diagnosis of 72 years;[1,2] its incidence and prevalence are expected to further increase in the short-term, proportionally increasing with the aging of the population.

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Chemo-immunotherapy regimens (eg, fludarabine cyclophosphamide rituximab, bendamustine plus rituximab, chlorambucil in combination with an anti-CD20 monoclonal antibody) have been the standard of care for many years. Yet, with the advent and introduction of novel targeted agents—including Bruton tyrosine kinase (BTK) and B-cell lymphoma-2 inhibitors—additional therapeutic options are now available, resulting in higher efficacy and a more favorable safety profile, providing the possibility of personalized treatment.[3] The opportunity for a tailored treatment is particularly essential for older patients, as aging is associated with more significant comorbidity and reduced functional reserve, negatively impacting patients' tolerance to treatments.[4–6] Thus, treatment choice may result challenging and, as such, requires shared decision-making involving both the physician and the patient with CLL. Efficient management must consider many factors, such as disease, chronological and physiological age, comorbidities, and concomitant medications.[5,6]

Few information is available about potential differences in the way patients and physicians rate the importance of efficacy, toxicity, and logistics of the administration for the choice of CLL treatment. Yet, knowledge of such preferences could improve share decision-making by guiding discussions among patients and physicians themselves. The identification and evaluation of preferences regarding the relative importance (RI) of attributes of treatments may be investigated with a discrete choice experiment (DCE): the latter may be applied to the healthcare setting to provide information on the factors driving a subject's

choice and willingness to accept trade-offs.[7–9] From an economic standpoint, by applying this method, professionals' preferences were investigated by Boqué et al,[10] showing the importance of cost, efficacy, and patient's age in choosing treatments for CLL. Furthermore, a DCE study was carried out in the United States among oncologists and patients investigating preferences for attributes associated with a novel treatment for CLL.[11] The main driving factor was efficacy, in terms of progression-free survival (PFS), for both groups of respondents; the risk of atrial fibrillation, infection, and discontinuation due to adverse events were also considered important.[11]

A DCE experiment has been performed in Italy, interviewing hematologists and patients with CLL and investigating attributes related to the efficacy, route of administration, schedule of visits, and tolerability of treatments. The following study aimed at further investigating how physicians and patients weigh attributes when selecting a treatment for CLL and managing the disease; the comparison of preferences in the 2 groups may therefore guide the treatment discussion and support addressing possible shortcomings.

MATERIALS AND METHODS

Study design

A preference questionnaire required forced choice between pairs of hypothetical treatments for CLL (Suppl. Material - Questionnaire). It was assumed that attributes describe treatments with levels and that individuals prefer combinations of attribute levels.

The board of experts (the authors of the present study) met 3 times to choose the attributes, which were initially selected based on a review of the available scientific literature on "CLL and DCE" and on the practical clinical experience of the scientific board members. The candidate attributes were afterward submitted to the experts of the Italian Association against Leukemias, Lymphomas and Myeloma (AIL). After the approval by the AIL and once a test version of the DCE questionnaire had been prepared, it was tested with a small group of their associates.

At the end of the selection and testing process, 7 attributes were chosen to characterize current, possible, and potential therapeutic options (Table 1).

Efficacy: (1) "Progression-free survival" (for patients, "Time before the disease reappears"). Levels were on a linear scale and represented PFS attributable to current therapies and (2) "Measurable residual disease" (for patients, "Persistence of leukemia cells at the end of therapy"). Two levels: "detectable" ("present" for patients) and "undetectable" ("absent" for patients).

Side effects: (1) Diarrhea. Three levels: 0 episodes, 1–2 episodes, and 3–7 episodes; (2) Severe infections, considering grades 3 and 4, that is, requiring hospitalization and/or IV antibiotic administration. Three levels of risk: 5%, 10%, and 15%; and (3) Atrial fibrillation. Four levels of risk: 0%, 5%, 10%, and 15%. Administration/management of therapy: (1) "Administration" concerns route (intravenous versus oral) and duration and includes 7 levels and (2) "Frequency of pre-planned hospital visits" (monthly, quarterly, half-yearly). Four combinations have been prohibited to prevent unrealistic profiles (eg, a period of 6 mo of intravenous therapy, with 6-mo visits).

After screening questions and informed consent, participants were asked about their disease and treatment histories. A fixed question with an obvious answer checked respondents' attention. The survey was tested in semistructured, face-to-face interviews with 10 patients.

Patients answered 8 DCE questions and clinicians 18 questions, choosing between pairs of experimentally designed hypothetical CLL treatments, each of them being a combination of the 7 attributes (Table 1) with different levels. We used Lighthouse Sawtooth software to generate the experimental design following good research practices in conjoint analysis and DCE. The different number of questions for patients and clinicians was due to the larger number of patients that could be reached compared with clinicians. In addition, clinicians may accept to answer more questions than patients, who, in turn, are more likely not to complete a survey with a large number of questions. As to sample size calculation, firstly, Orme's rule-of-thumb was applied. The minimum sample size necessary for the DCE was computed as $n \geq 500 \times c/ta$, where n is the number of respondents, c is the maximum number of levels per attribute (in our study, c = 7), t is the number of tasks (in our study t = 8 for patients and t = 18 for clinicians), and a is the number of alternatives (in our study, a = 2), resulting in n = 98 clinicians and n = 219 patients. Using simulated data, the Logit efficiency test documented that 70 clinicians answering 18 DCE questions and 200 patients answering 8 DCE questions allowed maintaining the standard error of preference weights below 0.10.

Table 1

Attributes Chosen for Evaluation in the Survey

Attribute Number	Attribute Label	Level Number	Level Label
1	Progression-free survival	1	24
		2	36
		3	48
		4	60
2	Mode of administration	1	Intravenous, for 6 mo
		2	Oral, for 12 mo
		3	Oral, for 24 mo
		4	Oral continuous
		5	Intravenous, for 6 mo + oral, for 12 mo
		6	Intravenous, for 6 mo + oral, for 24 mo
		7	Intravenous, for 6 mo + oral continuous
3	Frequency of pre-planned hospital visits	1	Monthly
		2	Quarterly
		3	Half-yearly
4	Diarrhea	1	0
		2	1–2
		3	3–7
5	Infections	1	5%
		2	15%
		3	30%
6	Atrial fibrillation	1	0%
		2	5%
		3	10%
		4	15%
7	Measurable residual disease	1	Detectable
		2	Undetectable

Sample

A convenience sample was recruited among associates of AIL between July 2020 and September 2021. The leukemia-lymphoma specialists e-mailed patients present in their database with an invitation and a link to the survey.

Analysis

The DCE questions generate panel data estimated using the main effects random-parameters logit (RPL) model with Lighthouse Sawtooth Software version 9.12.1. RPL accounts for differences in preferences across respondents that can bias results from conventional conditional logit models. Parameter estimates from the model can be interpreted as relative preference weights indicating the average relative preference for one attribute level over other attribute levels. The mean preference weights have been used to calculate each attribute's RI and the minimum acceptable benefit in terms of PFS months

required for respondents to accept a worsening of the other attributes.

RESULTS

Response rate and sample characteristics: patients

Target patients have been contacted through the website and the newsletter of AIL, and by doctors working with CLL patients posting announcements on social media. Notwithstanding those who immediately refused, 384 patients accessed the online survey and 215 provided consent and completed the survey—with the completion rate amounting to 58%, a close result to a similar DCE in CLL where it amounted to 62%. Table 2 presents descriptive statistics of the respondents' characteristics. The median age of patients was 66 years (minimum = 31, maximum = 88), about 60% were male, and the median time since diagnosis was 6 years (minimum = 0, maximum = 29).

In total, 85 patients (41%) were receiving treatments for CLL at questionnaire completion, and 44 of them (52%) were treated for the first time. A total of 99 patients (46%) declared to be previously treated for CLL. About one-third of patients (31%) responded that they were not currently on treatment or neither they had been in the past. The other demographic, clinical, and previous/current treatments information are reported in Table 2.

Table 2

Patients Summary Statistics (n = 215)

Characteristics	Statistics	
Age (y): median, minimum–maximum	66	31–88
Time since diagnosis (y): median, minimum–maximum	6	0–27
Time since first therapy (y): median, minimum–maximum	6	1–21
Sex		
Male	135	63%
Female	75	35%
Missing	5	2%
Education		
Primary	14	7%
Secondary	37	1%
High school	98	45%
College	60	28%
Missing	6	3%
Geographical area		
North Italy	61	28%
Center Italy	63	29%
South Italy	87	41%
Missing	4	2%
Temporal distance from home to the clinical center		
Less than 30 min	67	31%
30–60 min	79	37%
1–2 h	42	20%
More than 2 h	22	10%
Missing	5	2%
Ongoing treatment		
Yes	85	40%
If on treatment, first-line?		
Yes	44/85	52%
Which ongoing treatment		
Oral chemotherapy	19/85	22%
IV chemotherapy	0/85	0%
IV chemotherapy with monoclonal antibodies	5/85	6%
IV chemotherapy without monoclonal antibodies	0/85	0%
Only monoclonal antibodies	3/85	4%
New oral treatments	51/85	60%
Experimental drug	7/85	8%
Received treatment for CLL in the past?		
Yes	99	46%
Which previous therapy		
Oral chemotherapy	8/99	8%
IV chemotherapy	45/99	45%
Chemotherapy with monoclonal antibodies	41/99	41%
Chemotherapy without monoclonal antibodies	1/99	1%
Only monoclonal antibodies	1/99	1%
New oral treatments	9/99	9%
Experimental drug	4/99	4%

CLL = chronic lymphocytic leukemia; IV = intravenous.

Response rate and sample characteristics: clinicians

The target population of clinicians treating patients with CLL counted 183 doctors; 109 accessed the survey, and 69 completed the questionnaire. The median time since MD degree of the 69 clinicians was 26 years, and they reported long-standing expertise in clinical management of CLL, with 55% of them having more than 10 years of experience. The majority (67%) of the clinicians managed more than 100 patients with CLL. Clinicians' characteristics are summarized in Table 3.

Discrete choice experiment

As graphically represented in Figure 1, the first attribute in order of importance in orienting treatment preferences was the risk of severe infections for patients (RI 24%). In comparison, it was PFS for clinicians (RI 30%). The relative weight of the risk of serious infections was identical in the 2 groups (RI 24%), even though ranking second for clinicians.

Patients placed PFS in the third position with a RI (17%) lower than the mode/timing of administration (RI 20%). Clinicians placed the latter in the fourth position with a RI of 12%, while they attributed greater weight to diarrhea (RI 15%).

Table 3

Clinicians Summary Statistics (n = 69)

Characteristics	Statistics	
Time since MD degree (y): median, minimum–maximum	26	2–44
Sex		
Male	39	56.5
Female	30	43.5
Specialty		
Oncology	2	2.9
Hematology	60	87
Other	7	10.1
Experience on CLL management		
Less than 3 y	6	8.7
3–5 y	10	14.5
6–10 y	15	21.7
11–20 y	15	21.7
More than 20 y	23	33.3
Number of CLL patients managed		
Less than 20	1	1.4
20–49	3	4.3
50–99	19	27.5
More than 100	46	66.7
Type of clinical center		
Public	47	68.1
Private	8	11.6
Hospital	26	37.7
Academic	27	39.1
Role of respondent		
Unit director	5	7.2
CLL reference person	17	24.6
Other	47	68.1
Member of a scientific society		
Yes	53	76.8

CLL = chronic lymphocytic leukemia.

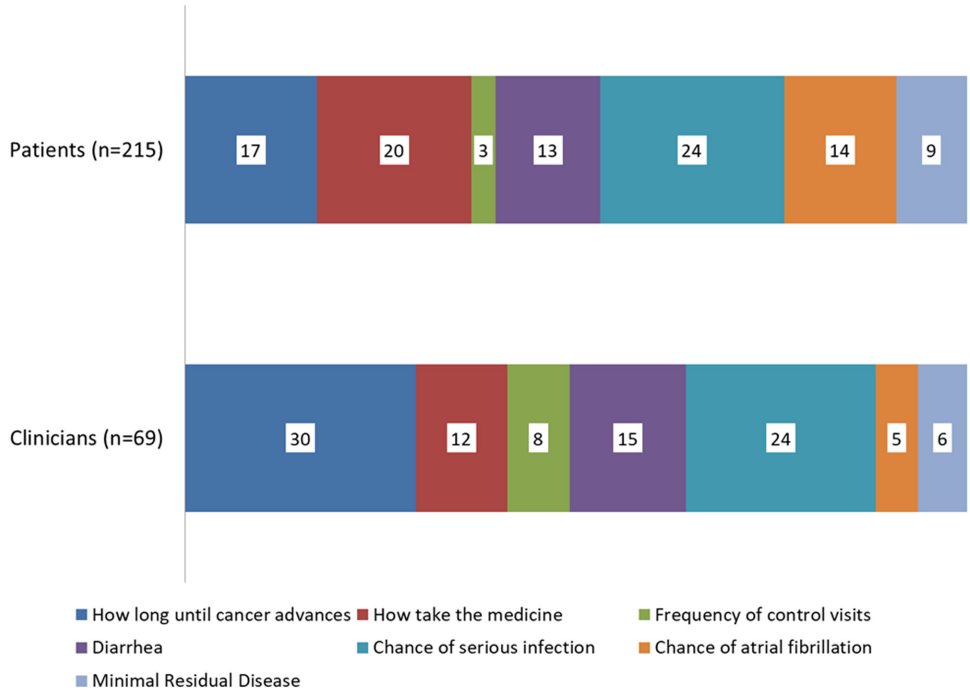

Figure 1. Relative importance of attributes for patients and clinicians.

The hierarchy of the importance of treatment-related side effects for patients was: (1) the risk of serious infections (RI 24%), (2) the risk of atrial fibrillation (RI 14%), and (3) diarrhea (RI 14%).

The hierarchy of the importance of treatment-related side effects for clinicians was: (1) risk of serious infections (RI 24%); (2) risk of diarrhea (RI 15%); and (3) risk of atrial fibrillation (RI 5%).

The frequency of pre-planned hospital visits did not have a relevant weight for both groups: RI 3% for patients and 8% for clinicians. The minimal residual disease (MRD) received a RI below 10%, with similar values for both groups.

The preference weights are represented in Figure 2. They indicate the relative strength of preference for each attribute level, where more significant positive numbers indicate a greater preference, and smaller negative numbers indicate a lower preference.

By examining the patterns of each attribute, the following considerations can be made. For patients, the differences between preferences across PFS levels were less pronounced. In particular, there was no significant increase in the preference for a 60 months-PFS compared with a 48 months-PFS. Clinicians' preferences are a linear function of PFS levels with a strong focus on maximum efficacy (60 mo) that clinicians may give up if the risk of severe infection is also at the highest level (30%). On the other hand, the 2 preference patterns for the mode/timing of administration were similar for both patients and clinicians. Oral therapies (with negligible differences between 12 and 24 mo) were preferred to intravenous administration (exclusive or in combination). The propensity towards oral therapy emerged statistically, except for continuous oral therapy for clinicians, as their preference index was positioned close to 0 ("indifference value"). Overall, the observed patterns indicate that the treatment duration weighs less than administration route.

The frequency of hospital pre-planned visits was entirely irrelevant for patients, while clinicians clearly preferred a quarterly frequency. As for the levels of diarrhea, the difference between the first 2 levels (0 and 1–2 discharges) was negligible for both clinicians and patients, while 3–7 discharges resulted in a significant disutility, especially for clinicians.

For severe infections, the patterns appeared similar to those seen for PFS. However, a 30% risk of serious infections was more unacceptable to clinicians than patients. On the other hand, the difference in patients' preference whether the risk of infections was 5 or 15% was smaller than that of clinicians. As far as the risk levels of atrial fibrillation and the presence/absence of MRD are concerned, patients and clinicians preferences were substantially overlapping.

According to the estimated preference weights, we estimated that patients would accept 3–7 diarrhea episodes (versus 0) if PFS increased by 28 months, while clinicians found it sufficient for PFS to increase by 18 months. Following the same approach, patients would accept a 25% additional risk of severe infections only if PFS increased by 50 months, while clinicians needed PFS to increase by 29 months to trade off this relevant side effect. Finally, patients would accept a 15% risk of atrial fibrillation (versus 0%) if PFS increased by 31 months, while clinicians only needed that PFS to increase by 6.5 months.

In the subgroup analysis (Suppl. Material - Subgroups Analyses: Figures S.01–S.11), differences based on clinicians' and patients' characteristics were examined. No statistically significant differences emerged between the preferences of any subgroup and the total sample or across subgroups. It should be noted that sample sizes were not computed based on an ad hoc power analysis and predefined relevant differences between subgroups. On the other hand, the observed differences were minimal, and the lack of significance could not be ascribed only to the underpowered analysis.

DISCUSSION

This cross-sectional survey investigated and compared the preferences among clinicians and patients with CLL for attributes of treatments. Attributes related to efficacy, administration and management, and adverse events were chosen for a DCE experiment based on conjoint analysis.

The DCE approach was used to obtain information that could help in shared decision-making, understand issues requiring patient education, and increase decision-maker awareness.

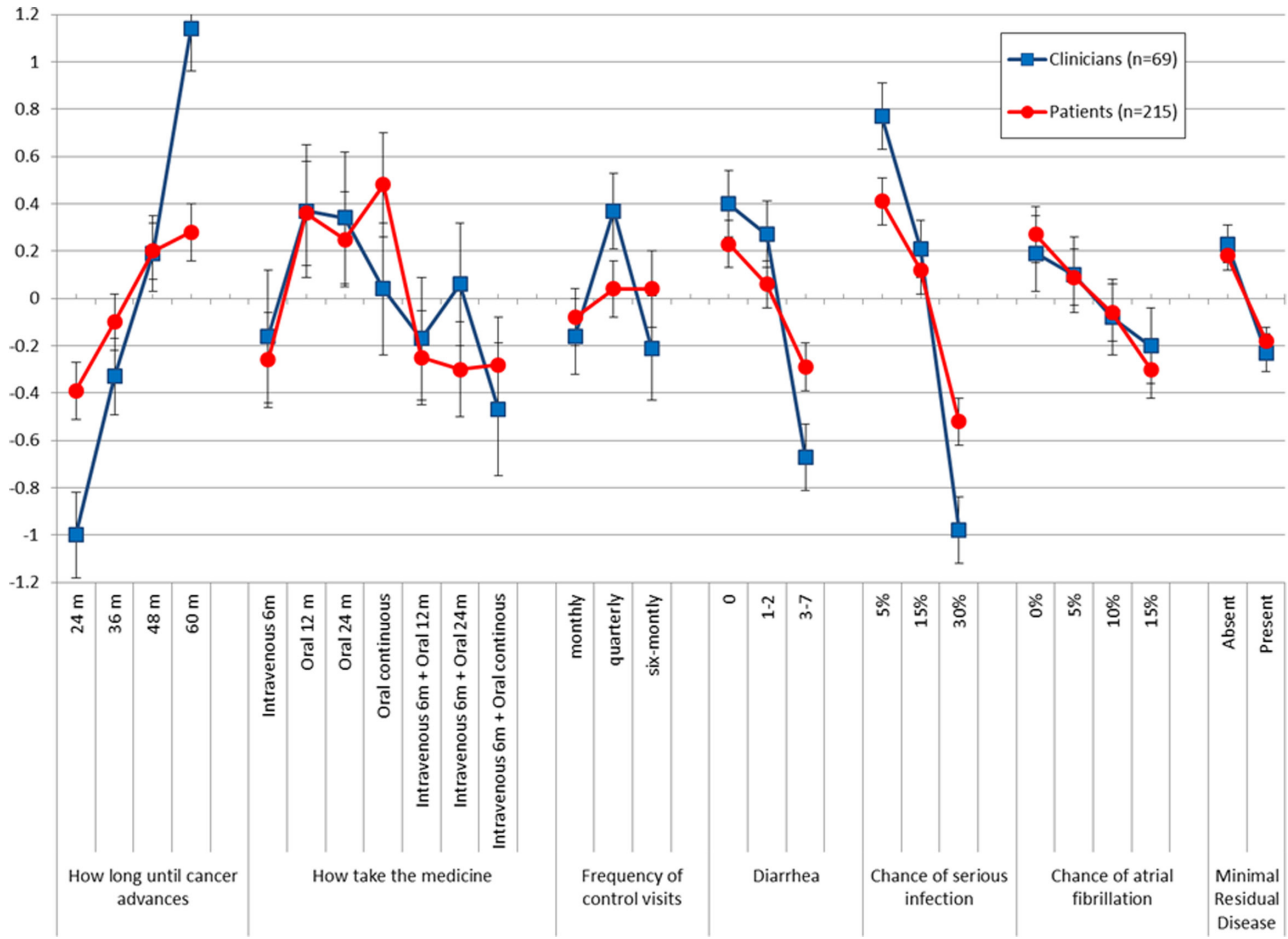

Figure 2. Preference weights of attributes for patients and clinicians. Preference weights indicate the relative strength of preference for each attribute level, where larger positive numbers indicate greater preference and smaller negative numbers indicate lower preference.

This method has been used in several studies on CLL, aiming to fill evidentiary gaps and obtain information for the design of services or the improvement of illness management.[12] For instance, Buchanan et al[13] reported a DCE survey that evaluated the preferences of UK CLL patients for pretreatment genetic and genomic testing: the results had implications for decision-making in both CLL and genomics' studies. In addition, the conjoint analysis may help to compare preferences of the different actors involved in CLL management, finding commonalities and inconsistencies, which may be valued in organizational perspectives.[10,11,14]

In our study, based on the preference weight, the most relevant attribute for clinicians was PFS, while it was the risk of severe infections for patients. PFS was the most crucial attribute in a DCE directed only to patients, but the risk of adverse events was also substantial.[12] The primary importance given by clinicians to treatment efficacy in terms of PFS in our study was in agreement with results reported in a US study by Le et al,[11] although only first-line treatment was considered in that case. Also, efficacy was characterized by a very high RI, although second to cost, in a DCE experiment evaluating hematologists' and pharmacists' preferences for treatment selection for CLL, showing a consistent evaluation of this attribute from a clinical and service organization perspective.[10] The relative weight of the risk of serious infections was identical in the 2 groups of our DCE. Le et al[11] also found that the risk of infections was important, yet not more than that of atrial fibrillation or treatment discontinuation due to adverse events. In our study, while the risk of atrial fibrillation was not relevant for clinicians compared with other treatment-related side effects, it was important for patients. Conversely, Le et al[11] found that atrial fibrillation was a greater concern for clinicians than for patients.

Interestingly, the clinicians participating in our study had limited concerns about atrial fibrillation, potentially reflecting that the majority of physicians reported more than 10 years of active management of patients with CLL, likely including the use of BTK inhibitor and the management of the related side effects. This contrasts with the deeper concern of patients for atrial fibrillation, suggesting that appropriate information to patients about the impact of cardiologic effects of drugs is needed to facilitate an informed treatment choice.

On the other hand, the fact that patients placed a great deal of emphasis on the risk of infections may reflect the historical period the survey was administered, that is, the severe acute respiratory syndrome coronavirus 2 pandemic. This may stem from the evident attention that not only health professionals but also the public media have given to the issue of prevention of viral infection and the importance of active immunization.

The caution in receiving treatments with a higher risk of immunosuppression can be considered a very likely consequence of the current pandemic, which created new awareness on the issue of infections that may last well beyond the pandemic's duration, impacting on the patient's preferences in the long run. It will be interesting to check possible shifts on this issue at the end of the emergency.

In our study, the mode of administration and management of treatment was also relevant, being placed in the second position

for patients and in the fourth position for clinicians. Treatment administration was more important for patients than physicians in a German DCE conjoint analysis, while it was not an essential attribute in the US study.[11,14] We observed that both groups of respondents preferred the oral administration, even if continuous, compared with the intravenous therapy if it was associated with prolonged PFS. In contrast, the duration of therapy was less relevant for both groups. Interestingly, the frequency of appointments was negligible for patients, while clinicians indicated a preferred option for a quarterly frequency of pre-planned visits. This, again, may reflect a different perception of the aim and value of the pre-planned visits. As long as patients feel safe on an effective drug, the number of visits is likely considered appropriate to their needs in each case based on the physician's evaluation. In contrast, clinicians associate the frequency of the pre-planned visits with the difficulty of managing a therapy and, ultimately, the frequency of adverse events.

Our results show that the efficacy, safety profile, and treatment-related quality of life, in terms of oral administration, of novel targeted agents are in line with both physicians' and patients' expectations, becoming strong drivers of treatment choice.

We must also acknowledge that patients' possible misunderstanding of attribute importance is a limitation of the method. Indeed, the DCE approach may include a limited number of attributes, but it has been demonstrated that it is possible to evaluate the impact of an additional attribute by a follow-up question; this opens the possibility of further investigation.[15]

Another possible limitation consists of the fact that we did not reach the exact planned number of respondents and thus the precision of preference estimates was slightly reduced. In addition, our sample seems to be drawn from a population younger (median age = 66 y) than that expected of CLL patients (around 70 y). This can be due to an easier access to digital tools (as the questionnaire was administered online) of younger patients: this may lead to selection bias. On the other hand, we checked the possible effect of age (less or more than the median) on preferences and no evidence of differences emerged.

In summary, for both patients and clinicians, the effectiveness of therapy takes priority in the treatment choice. However, the prevention and optimal management of adverse events related to treatment remain of key importance. At the time of treatment choice, a careful risk-benefits evaluation of the different treatment options is essential and should be conducted in close relationship with patients taking into consideration their preferences, only after adequate information and education have been provided.

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AUTHOR CONTRIBUTIONS

All authors supervised the questionnaire preparation, interpreted results, prepared, revised, and approved the article. PP planned the research and analyzed data.

DISCLOSURES

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