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Treatment decision-making in chronic lymphocytic leukaemia: Key factors for healthcare professionals. PRELIC study

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ABSTRACT

Objective: To explore the preferences of Spanish healthcare professionals (haematologists and hospital pharmacists) for the treatment selection of active Chronic Lymphocytic Leukaemia (CLL) patients at first relapse, condition that mainly afflicts older adults.
Methods: A discrete choice experiment (DCE) was conducted among haematologists and hospital pharmacists. A literature review and a focus group informed the DCE design. CLL treatment settings were defined by seven attributes: four patient/disease-related attributes (age, functional status, comorbidities, and risk of the disease) and three treatment-related attributes (efficacy [hazard ratio of progression-free survival, HR-PFS], rate of discontinuations due to adverse events and cost). A mixed-logit model was used to determine choice-based preferences. Relative importance (RI) of attributes was calculated and compared between stakeholders. Willingness-to-pay (WTP) was estimated through the DCE. Besides, nine ad-hoc questions were posed, to explore more in depth CLL treatment decision making.
Results: A total of 130 participants (72 haematologists and 58 hospital pharmacists) answered the DCE. All attributes were significant predictors of preferences ($p < 0.05$) in the multinomial model. Higher RI was obtained for treatment-related attributes: the highest rated being 'cost' (23.8%) followed by 'efficacy' (20.9%). Regarding patient-related attributes, the highest RI was obtained for 'age' (18.1%). No significant differences ($p > 0.05$) in RI between haematologists and pharmacists were found. WTP for the treatment was higher for younger CLL patients. Ad-hoc questions showed that patient age and functional status influence treatment decisions.
Conclusions: For healthcare professionals, 'cost' and 'efficacy' (treatment-related attributes) and age (patient-related attribute) are the main factors that determine CLL treatment selection at first relapse. WTP decreases as patient's age increases.

1. Introduction

Chronic lymphocytic leukaemia (CLL) is the most common leukaemia in the Western world [1]. It typically afflicts older adults [2], with a median age at diagnosis of 72 [1]. With the rapid ageing of the population, the incidence and prevalence of CLL among older persons is expected to continue to increase.

Treatment of older patients remains complicated due to multiple factors, such as the variability in fitness [3], cognition and comorbidities [2]. Particularly, treatment of relapsed CLL is highly personalized due to the advanced age of the patient population, the risk of severe adverse events (AEs), and the often chronic nature of this disease [4]. Traditional intensive chemotherapy treatments for CLL can be difficult for older patients to tolerate [2,5]. More recently, novel oral agents are proving to be both well tolerated and effective in this population, redefining the field of CLL therapy. Finally, new treatments and combination therapies currently undergoing further study have

Abbreviations: AEs, Adverse events; CLL, Chronic lymphocytic leukaemia; DCE, Discrete-choice experiment; HR-PFS, Hazard ratio of progression-free survival; NHS, National health system.

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potential utility in older patients with CLL [2], and the capacity to modify the natural course of the disease [6].

Treatment choices for older patients must account for the interactions of disease, age, and therapy, since ageing involves a progressive decline in functional reserve and greater comorbidity; all these factors combine to reduce life expectancy and tolerance of stress [7,8]. These changes are universal, but occur at different rates in different individuals; hence age alone is a poor prognostic factor for life expectancy and CLL treatment tolerance [3,7]. Therefore age should not be the sole determinant in decision-making and choice of therapy [9]. Ageism is discriminating against individuals or groups on the basis of their age [10] and is a topic that has been studied at length in the field of oncology [11], since it is an attitude frequently observed in health professionals [12]. To rely totally on chronological age in making treatment decisions is ethically inappropriate [13,14]. Nowadays, the assessment of physiological age, its influence on treatment tolerance, and personalized treatment of CLL are emerging as key issues in the management of CLL in older patients [7,8].

Cost considerations have also been described to be a factor in treating older CLL patients [15]. In National Healthcare Systems (NHS) with public funding, like the Spanish NHS, the Sistema Nacional de Salud (SNS), prescribing physicians can be considered as double agents acting as patients' advocates but also as society's gatekeepers of resource use. On the one hand, public healthcare organizations put pressure on physicians to control pharmaceutical spending and, on the other hand, doctors are patients' agents and as such prescribe treatments that maximize the utility, effectiveness and quality of care in the face of economic restrictions [16]. In the hospital setting, the decision of incorporating drugs in formulary is the responsibility of the Pharmacy and Therapeutics Committee [17]. In this regard, some cost awareness studies have suggested that physicians only have an approximate knowledge of drug prices [16] and tend to neglect price differences between products of identical composition [18]; while other findings show that doctors feel pharmaceutical costs are important [16,19].

Healthcare professionals' preference over alternative treatments can be addressed through the discrete choice experiment (DCE), a common technique to elicit individual preferences for health care services or technologies [20]. The DCE allows for aproximation of the decision-making process performed by patients and professionals in real life. It consists of presenting the participants with a free choice of two hypothetical treatment options (scenarios), determined by different characteristics. The answers are analyzed to estimate the relative importance (RI) of the investigated attributes in the choice of treatments [21].

A few studies have explored patients' or professionals' preferences for the treatment of onco-haematological malignancies, mostly related to treatment efficacy or AEs. However, to our knowledge, neither the importance of drug cost nor patient-or disease-related attributes have been previously considered in preference elicitation studies in CLL, despite they constitute key factors in treatment decision-making.

The aim of PRELIC study is to explore the preferences of Spanish healthcare professionals (haematologists and hospital pharmacists) for the selection of treatment for CLL patients at first relapse through a DCE. Although health professionals are not decision makers in the price and reimbursements processes within the SNS, we investigate how important different attributes of the therapeutic scenario of CLL are for them, and what factors determine their preferences, in regards to both the patient and therapeutic characteristics. In particular, we focus on patient's advanced age as a possible decision bias, and on the cost of the drug.

2. Materials and Methods

2.1. Study Design and Participants

PRELIC is an observational study developed in the Spanish healthcare setting. The participants of the study were professionals in the field of haematology and hospital pharmacy from the SNS. Haematologists were eligible if they had at least two years of professional experience, their professional time dedicated to clinical assistance was over 70%, and they had expertise in CLL patients. Pharmacists were eligible if they had at least two years of professional experience and were familiar with onco-haematological drugs.

The minimum sample size necessary for the DCE was established according to the recommendation proposed by Orme [22]: $n \geq \frac{500c}{ta}$, where n is the number of respondents, c is the maximum number of levels per attribute, t is the number of tasks, and a is the number of alternatives per task.

Professionals were invited to participate through the Spanish Society of Haematology and by a direct invitation to the pharmacy service of hospitals and clinics. Therefore, the total number of professionals invited was not known. They were requested via email to complete a questionnaire (Supplementary Table S1) administered on a dedicated study website. The study questionnaire was available from March to May 2017.

A multidisciplinary scientific committee constituted by experts in haematology ($n = 2$), hospital pharmacy ($n = 2$) and health economy ($n = 1$), each with >15 years' professional experience, provided scientific advice during the development of the study.

2.2. Discrete-Choice Experiment (DCE)

Stated-preference surveys are one of the most reliable and valid techniques available for quantifying participants preferences. The most commonly used stated-preference format in health care is the DCE [23]. The DCE allows the identification and evaluation of participants' preferences for treatment and their relative importance in decision making [24]. Respondents are presented with several treatment choice sets, each one comparing two hypothetical treatment options (scenarios) and are asked to choose between them. Each choice set consists of multiple hypothetical profiles consisting of a fixed set of criteria (attributes), with varying values (levels) between the profiles [25]. The DCE allows for the estimation of overall preferences for any combination of attributes and is shown to be one of the most sensitive methods to elicit preferences, so the DCE is considered to better reflect actual decision making than rating scale exercises [26]. The DCE was developed according to good research practices recommended by International Society for Pharmacoeconomics and Outcomes Research (ISPOR) [27].

2.2.1. Identification of Attributes and Levels

Attributes and their associated levels were initially identified from literature review. After, a focus group with the scientific committee to assess the relevance of the potential attributes identified in the literature, to identify attributes not retrieved in the literature and finally to assess the comprehensibility of the attributes and levels proposed. The result of literature review and the focus group produced seven attributes with a maximum of three levels each (Table 1). Various reasons lay behind the final selection of these attributes. The “age” attribute was limited to elderly patients (70, 75 and 85 years). Two attributes (genetic alterations and relapse) were redefined into one (“risk of the disease”), according to the group criteria for patients at relapse proposed in ESMO guidelines and in the Spanish national guidelines for the management of patients with CLL [1,28]. The range of drug costs was chosen taking into account the annualized list prices of the main drugs used for relapsed CLL in 2017 in Spain. Hospital medicines or hospital-dispensed medicines are fully reimbursed in Spain; therefore, no out-of-pocket expenses are expected from the patients.

2.2.2. Experimental Design

Experimental design techniques were then used to construct a series of choice tasks from combinations of the attribute levels (called scenario alternatives). The design was orthogonal (each pair of levels appears

Table 1
Attributes and levels included in the scenarios.

	Attributes	Levels
Patient/Disease	Age (years)	70 75 85
	Performance status	Good (ECOG 0-1) Poor (ECOG ≥2)
	Comorbidities	No comorbidities Renal failure (with or without other comorbidities) Other comorbidities (with functional repercussion and normal renal function)
	Risk of the disease	Low [without 17p-deletion/p53 mutation and late relapse (>3 years)] High [with 17p-deletion/p53 mutation and/or early relapse (<3 years)]
Treatment	Efficacy (HR-PFS)	HR = 0.30 (70% reduction in the risk of progression or death) HR = 0.45 (55% reduction in the risk of progression or death) HR = 0.65 (35% reduction in the risk of progression or death)
	Discontinuation due to AEs	5% 15% 25%
	Cost	€10,000/year €35,000/year €70,000/year

ECOG: Eastern Cooperative Oncology Group; HR: Hazard Ratio; HR-PFS: Hazard Ratio of Progression-Free Survival; AEs: Adverse Events.

equally often across all pairs of attributes within the design) and balanced (each level of an attribute occurs the same number of times) [24]. The fractional factorial analysis (main effects orthogonal matrix) generated 36 scenarios, with a mix-and-match algorithm being used to generate the choice sets. Dominated scenarios were identified and minimized. To avoid participant fatigue, the 36 scenarios were distributed among three versions of questionnaires of 12 multiple-choice sets. Each participant received a randomly assigned version of the questionnaire. Every task required to choose between two scenario alternatives (Supplementary Table S2).

2.3. Ad-hoc Questions

Nine ad-hoc questions were included in the questionnaire to complement the information of the DCE. The questions raised were based on the contributions of the scientific committee about the most relevant attributes for decision-making in CLL. This included three questions about the importance given to age, four about functional status, and two to estimate the willingness-to-pay (WTP) in a situation of therapeutic choice in CLL (Supplementary Table S1).

In question 1, professionals were asked about the "Importance of patient's age when making decisions or recommendations about pharmacological treatment in CLL" using a Likert scale from 1 (not important) to 5 (very important). The range "important" was defined as the values 4 (important) and 5 (very important) of the scale, and "not important" as the values 1 (not important) and 2 (slightly important).

In questions 2–3, professionals assessed the "Frequency in which patient's advanced age modifies the therapeutic regimen indicated/recommended for CLL" and the "Frequency in which patient's advanced age impedes/hinders active treatment", respectively, using a Likert scale from 1 (never) to 5 (always). In question 2, the range "modifies" was defined as the values 3 (sometimes), 4 (frequently) and 5 (always) of the scale, and "does not modify" as the values 1 (never) and 2 (rarely). In question 3, the range "prevents/hinders" was defined as the values 3 (sometimes), 4 (frequently) and 5 (always), and "does not prevent/hinders" as the values 1 (never) and 2 (rarely).

In questions 4–7, participants indicated the specific value for age in each situation. In questions 8–9, participants indicated their preferences regarding the cost in a scale from a reference cost of €20,000 to ≥ €100,000, using intervals of €10,000.

2.4. Survey Instrument

The questionnaire consisted of four parts: (i) screening questions (selection criteria), (ii) sociodemographic data, (iii) preferences (DCE) and (iv) ad-hoc questions. To avoid response bias due to the framing effect of question sequence, the order of ad-hoc questions about younger and older patients were randomized in the questionnaires.

2.5. Statistical Analysis

2.5.1. DCE

Based on respondents' answers to the series of choice questions, the mixed logit model was applied to calculate the preference weights for all attribute levels, using Stata software [29]. The model relates the probability of choosing one treatment over another to observable differences between treatment options. The model accounts for preference heterogeneity among respondents. It yields both a mean effect and a standard deviation (SD) of effects across the sample [30]. The dependent variable was choice, whereas independent variables were the attribute levels.

The mixed logit model was firstly considered with all the variables as categorical, except the cost, which was considered linear to estimate WTP. In a second model, the attributes age, treatment efficacy and discontinuation for adverse effects were considered as linear variables. The two models were compared using the Akaike Information Criterion and the Bayesian Information Criterion [31]. In both cases, values obtained for the linear model were lower than those obtained for the categorical model, indicating that the linear transformations provided a better adjustment.

The regression estimates from the mixed logit model are interpreted as the utilities associated with each respective attribute level and referred to as part-worth utilities, which represent the relative contribution of changes in treatment attributes to the choice. A higher part-worth utility for a specific attribute level indicates a greater likelihood that a treatment scenario including that attribute level will be chosen, all else being equal. Part-worth utilities were subsequently used to estimate RI of each studied attribute. RI was calculated as the percentage ratio of the utility difference between the highest and lowest levels within each attribute to the sum of differences between the highest and lowest levels across all attributes in total. RI ranges from 0 to 100% per attribute (sum to 100% across all attributes) [32]. The inclusion of a cost attribute in the DCE allows for a monetary estimate of utility, the WTP [33], by applying the methodology of the marginal rate of substitution [34]. This method consists in dividing the part-worth utility of the attribute levels (in this case, age [per year], efficacy [HR-PFS] [1%] and % discontinuation due to AEs [1%]) by the part-worth utility of the additional cost per month; and expressed in absolute value.

2.5.2. Subgroup DCE Analysis

Professional specialty (haematology and pharmacy) and time of experience were studied as possible explanatory variables for the preferences, estimated independently for each participant. Traditional parametric independent *t*-tests or the non-parametric Mann-Whitney *U* test, according to data distribution, were used to assess whether RI of attributes differed between groups. Regarding time of experience, two subgroups were established from the cut-off point of mean years of professional experience of the sample: professionals with lower or higher time of experience than the mean of participants. Preferences based on time of professional experience were then analyzed and compared from the total of participants and by specialty subgroups (haematologists and pharmacists).

2.5.3. Ad-hoc Questions

The importance given to age in treatment decision-making was described by relative and absolute frequencies of the responses. The age limit for treatment recommendation according to performance status was estimated as mean (SD). WTP from hypothetical scenarios was described by relative and absolute frequencies of response and by weighted mean values.

3. Results

3.1. Demographic Characteristics

A total of 130 professionals from the different Spanish regions completed the electronic questionnaire and were included in the final data analysis. Of these, 72 (55.4%) were haematologists and 58 (44.6%) were pharmacists. Participants' characteristics are presented in Table 2. This sample size accomplishes the minimum number of participants according to the sample estimation, n ≥ 500c/ta, where c is the maximum number of levels per attribute (three), t is the number of tasks (36 tasks), and a is the number of alternatives per task (two).

3.2. Discrete Choice Experiment

3.2.1. Preferences

Table 3 and Fig. 1 present the results of the analysis of professionals' preferences for the treatment scenario in CLL. All attributes were statistically significant determinants of professionals' preferences ($p < 0.05$).

Among all participants, higher RI was obtained for treatment-related attributes, the highest rated being 'cost' (23.8%) followed by 'efficacy' (hazard ratio of progression-free survival, HR-PFS) (20.9%). Regarding patient-related attributes, the highest RI was obtained for 'age' (18.1%) (Table 4).

3.2.2. Willingness-to-Pay

Professionals' WTP calculated from the DCE for the attributes age, efficacy (HR-PFS) and % discontinuation due to AEs is shown in Table 5. WTP for CLL treatment increases for any of the following: lower patient age, higher PFS or lower discontinuation rates due to AEs.

3.2.3. Factors Defining Preferences: Subgroup Analysis

In the analysis of preferences by specialty subgroup, no significant differences in attributes RI were found between haematologists and pharmacists (Table 4).

Two groups were established according to mean time of professional experience (16.6 years): professionals with <17 years of experience (n = 64) and professionals with ≥17 years of experience (n = 66). Subgroup analysis of mean attribute importance revealed that professionals with larger experience gave stronger preference to "age" ($p < 0.042$) (15.6% those with <17 years of experience, and 18.7% those with ≥17 years of experience) (Supplementary Table S3).

The analysis of preferences between haematologists with an experience <17 years (n = 33) and ≥ 17 years (n = 39) revealed significant differences, with higher RI given to "age" ($p < 0.040$) and lower RI given to "% discontinuation due to AEs" by those professionals with higher time of experience ($p < 0.026$). The analysis of preferences in pharmacists with an experience <17 years (n = 31) and ≥17 years (n = 27) showed no significant differences (data not shown).

Table 3
Professionals' preferences.

Attribute	Level	Coefficients	SE	p-value
Age (years)	Per year	−0.123	0.017	0.000'
	70	−8.608	–	–
	75	−9.223	–	–
	85	−10.453	–	–
Performance status	Good (ECOG 0–1)	0	–	–
	Poor (ECOG ≥2)	−1.195	0.173	0.000
Comorbidities	No comorbidities	0	–	–
	Renal failure (with or without other comorbidities)	−0.328	0.148	0.027
	Other comorbidities (with functional repercussion and normal renal function)	−0.532	0.176	0.003
Risk of the disease	Low	0	–	–
	High	0.753	0.197	0.000
Efficacy (HR-PFS)	1% reduction in the risk of progression/death	0.061	0.007	0.000'
	HR = 0.30 (70% reduction in the risk of progression/death)	4.263	–	–
	HR = 0.45 (55% reduction in the risk of progression/death)	3.349	–	–
	HR = 0.65 (35% reduction in the risk of progression/death)	2.131	–	–
Discontinuation due to AEs	1%	−0.066	0.009	0.000'
	5%	−0.329	–	–
	15%	−0.988	–	–
	25%	−1.647	–	–
Cost	€1/month	−0.000^	0.000	0.000
	€833.33/month (€10,000/year)	0.404	–	–
	€2916.67/month (€35,000/year)	−1.413	–	–
	€5833.33/month (€70,000/year)	−2.826	–	–

'Age, efficacy and discontinuation due to adverse effects were considered as linear variables, as linear transformations provided a better adjustment than the categorical mixed-logit model. ^*0.00048;* AEs: % of discontinuation due to adverse events; HR-PFS: Hazard Ratio of Progression-Free Survival; SE: Standard error.

3.3. Ad-hoc Questions

Questions 1–3: 90.7% of participants considered age to be important when making decisions about CLL treatment, while only 4.6% considered that age is irrelevant for therapeutic decisions. 93% of participants considered that age modifies the recommended therapeutic regimen for CLL. Additionally, 77.7% of participants expressed a view that the patient's age hinders access to active treatment.

Questions 4–7: In patients with good performance status, professionals would recommend treatment with chemo-immunotherapies up to 80.9 (SD: 9.2) years. On the other hand, treatment with targeted therapies would be recommended until later ages (86.5 [SD: 8.5] years). When patient performance status is restricted, the age of recommendation of active treatment for CLL decreases, recommending

Table 2
Participants sociodemographic characteristics.

		Total (n = 130)	Haematologists (n = 72)	Pharmacists (n = 58)
Gender, male (%)		**45.4**	38.9	53.4
Age, years (mean, SD)		**45.6 (8.4)**	46.2 (7.5)	44.7 (9.4)
Professional experience, years (mean, SD)		**16.6 (8.4)**	16.8 (7.7)	16.3 (9.3)
Practice setting	Public (%)	**93.1**	90.3	96.6
	Public-private (%)	**6.9**	5.4	3.4
Position (%)	Head of department (%)	**31.5**	20.8	44.8
	Associate (%)	**68.5**	79.2	55.2
CLL patients per year (mean, SD)		–	72.1 (71.1)	–

Results for the whole sample of participants are highlighted in bold.

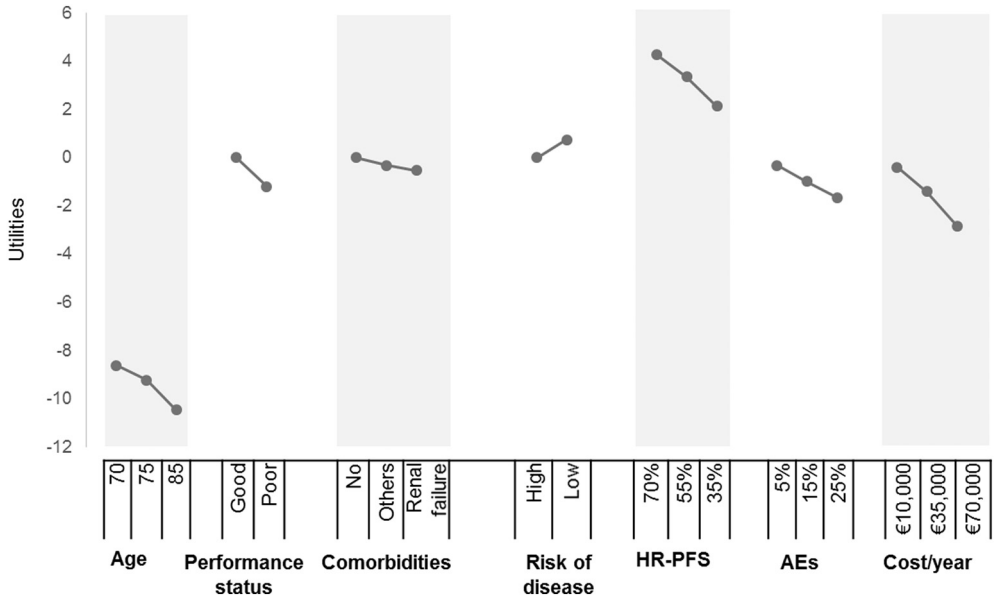

Fig. 1. Part-worth utilities within attributes. (utilities associated with each attribute level). AEs: % of discontinuation due to AEs. HR-PFS: hazard ratio of progression-free survival.

chemo-immunotherapies up to 75.2 [SD: 10.7] years and targeted therapies up to 82.1 [SD: 9.6].

Questions 8–9: When considering a treatment offering a 1 year-PFS gain with respect to standard treatment; professionals expressed that the Spanish SNS should pay 12.3% less for the treatment in patients aged ≥80, compared to patients aged 70 (€36,769 vs. €41,923 per year, respectively). In patients aged 70, 15.3% of professionals considered that it would be acceptable to pay ≥€60,000 for the treatment, whereas only 7.6% consider this range acceptable in patients ≥80 years. Detailed results for ad-hoc questions are shown in Supplementary Table S4.

4. Discussion

CLL is a disease of old age [35], and its incidence and prevalence are expected to increase with the ageing of the population. In this context, there is a need to identify the factors that drive treatment decision-making for this population group, in order to provide them with the best treatment strategies.

In this study, a DCE was carried out to assess the importance conferred by healthcare professionals (haematologists and pharmacists) to the characteristics of the therapeutic scenario at first relapse of CLL. A total of 130 participants (72 haematologists and 58 pharmacists) answered the study questionnaire. Cost (RI: 23.8%), efficacy (RI: 20.9%) and age (RI: 18.1%) were found to be the most important factors for professionals when making decisions about CLL treatment. The preferred treatment would be that with lower cost, higher efficacy, and for a younger patient.

In many countries, pricing and public financing decisions are driven or supported by economic evaluation studies. However, it is arguable whether decisions should be guided by cost-related preferences in decision makers or even in health professionals. The American College of Physicians outlined that health resource allocation decisions must focus on medical efficacy, effectiveness, and need, with consideration of cost based on the best available medical evidence [45]. In line with this, cost-consciousness has been widely studied in scientific literature. Some studies have stated that doctors have a limited or inconsistent understanding of therapeutic costs [36–38]. On the other hand, it has also been found that doctors' stated cost-consciousness appears to be generally high, and many decisions regarding medical treatments are influenced by factors other than the expected benefit to the patient, including concerns about cost and income [39]. Knowing what influences physicians' attitudes toward health care costs is an important matter, because most health care expenditures are the results of doctors' decisions [37]. This study confirms that cost is important for healthcare professionals when making decisions about CLL treatment. High costs of new CLL therapies might have influenced these preferences.

From the DCE, we also found that WTP for the treatment depends on patients' age, being lower for older patients. In this study we do not explore the reasons why this happens. Considering the literature, there could be at least two explanations. First, health professionals might perceive that the value of some health states, and consequently the value of the drugs aiming to correct them, are lower in older patients than in

Table 4
Relative importance of attributes.

Attribute	Total (n = 130)	RI haematologists (n = 72)	RI pharmacists (n = 58)	p-value (haematologists vs. pharmacists)
Cost	**23.8%**	20.4%	21.7%	0.529[a]
Efficacy (HR-PFS)	**20.9%**	20.7%	17.7%	0.063[b]
Age	**18.1%**	16.6%	17.9%	0.366[a]
AEs	**12.9%**	12.9%	12.5%	0.164[b]
Performance status	**11.7%**	10.7%	11.7%	0.239[a]
Risk of the disease	**7.4%**	11.4%	12.0%	0.540[b]
Comorbidities	**5.2%**	7.3%	6.5%	0.104[b]

Results for the whole sample of participants are highlighted in bold.
[a] t-test.
[b] Mann-Whitney U test; AEs: % of discontinuation due to AEs; HR-PFS: Hazard Ratio of Progression-Free Survival.

Table 5
Willingness-to-pay (WTP).

Attribute	Unit	WTP/month[a]
Age	↓1 year	€253.9
Efficacy (HR-PFS)	↑1%	€125.7
% discontinuation due to AEs	↓1%	€136.0

AEs: % of discontinuation due to adverse events; HR-PFS: Hazard Ratio of Progression-Free Survival.

[a] WTP for each attribute was estimated dividing the part-worth utility of the attribute levels (in this case, age [per year], efficacy [HR-PFS] [1%] and % discontinuation due to AEs [1%]) by the part-worth utility of the additional cost per month; and expressed in absolute value.

younger counterparts [40,41]. A second explanation might be that, even considering that the value of the drug was the same regardless of age, health professionals felt compelled by a utilitarian ethic to maximize social benefit by allocating the most expensive resources to younger patients [42]. Of note, the greater RI assigned to chronological age than to performance status is a fundamental issue in geriatric oncology. A primary determination when considering the appropriate therapy for an older patient with cancer is patient's physiologic age (which assesses, among others, comorbidity and functional status) rather than chronologic age [43].

This study emphasizes the importance of taking into account patient-centered aspects in decision-making about CLL treatment, including both patient/disease and treatment attributes in the therapeutic scenario of CLL. It is widely described in the literature that the assessment of patient-related factors, such as age, comorbidities and functional status, is of crucial importance for an optimal treatment choice in CLL [3,7,8,44]. At the same time, a few DCE studies have analyzed the role of drug cost in determining treatment selection preferences in oncology [45–47]. However, to our knowledge, this is the first DCE study including both patient-related characteristics and drug cost as attributes for CLL treatment selection. Therefore, the importance given to the combination of these factors in health professional preferences had not been previously quantified.

An important limitation of a DCE study is that other attributes not included may also be relevant and different levels may provide other part-worth utilitity values and relative importance. However, we tried to prevent this potential bias by selecting the most important attributes from the literature, using the input of an expert panel. Moreover, it is not known whether these unconscious preferences translate to prescriptions [48] or into different patterns of choices in real practice. Therefore, the study participants might make other choices in real life. It has to be also noted that no information exploring the ethical issues about balancing the dual role of participants as patient advocates and gatekeepers of system resources was collected. Sample size requirements in DCE are also a controversial issue. No general recommendations exist, so sample sizes differ substantially between studies and the method used is not usually reported [49]. This study followed the well-established recommendations proposed by Orme [22]. According to the survey method employed, the number of professionals invited was not known and therefore response rate cannot be estimated. Finally, the findings of the study significantly reflect preferences of healthcare professionals in Spain and should be interpreted within their context. In any case, data provide new insight into treatment decision-making in CLL.

Ad-hoc questions allowed us to explore in more detail the characteristics of CLL treatment considered most relevant by experts, including age, functional status and WTP. The vast majority of participants (90.7%) considered that age is important when making decisions about CLL treatment. For 93%, age modifies the recommended therapeutic regimen; while 77.7% find older age impedes access to active treatment. Functional status is a limiting factor for accessing treatment approaches in CLL, restricting the provision of active treatment and determining the type of therapy. In this sense, despite a low RI was assigned to performance status when considered jointly in the DCE, this attribute is a significant determinant of preferences, and therefore, ad-hoc questions show that it influences CLL decision-making. For patients with good functional status, chemo-immunotherapy was recommended up to 80.9 (SD: 9.2) years, while in those with limited status only up to 75.2 (SD: 10.7) years. With regard to new targeted therapies, they were recommended up to 86.5 (SD: 8.5) years for patients with good condition and up to 82.1 (SD: 9.6) years for patients with functional limitation. The additional questions further confirmed that patient age has an impact on health professionals' monetary utility of CLL treatment, in line with the results obtained from the DCE. Hence, professionals considered that monetary utility of the treatment for the SNS in young patients is greater than in older patients. That would suggest health professionals might consider acceptable a higher price paid by the SNS for younger patients than for older patients. Analysis regarding ad hoc questions looking at the WTP is limited by the reference cost used and the frequency of the interval of prices give to health professionals. However, the reference cost (€20,000) was chosen based on real annual cost of CLL treatment in Spain and the intervals of €10,000 provide an ample range of values to health professionals.

5. Conclusion

The study shows that for the evaluated Spanish healthcare professionals, when making treatment decisions for CLL patients at first relapse, treatment cost is the most important attribute, followed by PFS and age. Age is a crucial factor, WTP for the treatment being lower in older patients. It remains to be seen if these results, and results from similar studies, will impact in future guidelines regarding therapeutic decision-making in CLL, and whether those guidelines will take into account physiological age (instead of chronological age), cost/effectiveness and treatment allocation. Extensive further research is warranted to ascertain if the findings are confirmed in other oncological diseases of the elderly. That would provide a wider vision on whether health professionals' preferences point to cost before age and that affects their decision-making process. Audits of drug utilization should address whether older patients are being treated according to guidelines to the same extent as younger ones. Finally, where economic evaluation is used for pricing and financing, if studies confirmed different values of treatment by physiological age, more research would be needed on equity and financial aspects of establishing differential pricing and reimbursement schemes reflecting those differences.

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Ethical Statement

The study was approved by the Ethics Committee (CEIC) of Bellvitge University Hospital.

Conflicts of Interest

Gabás-Rivera C and Lizán L work for an independent research entity and have received fees for their contribution to the development of the project and the writing of the manuscript. Boqué C, Abad MR, Agustín MJ, García-Goñi M and Moreno C have participated in advisory meetings for the study. Granados E and Pardo C work in Gilead Sciences. Castro-Gómez A has worked in Gilead sciences. All authors have approved the final article.

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Appendix A. Supplementary Data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgo.2019.03.010.

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