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STUDY REVIEW

Patient preferences for chronic lymphocytic leukemia treatments: A discrete-choice experiment

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Independent expert commentary by Professor Chan Cheah

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Abbreviations used in this review:

BTKIs = Bruton tyrosine kinase inhibitors; **CI** = confidence interval; **CIT** = chemoimmunotherapy; **CLL** = chronic lymphocytic leukaemia; **DCE** = discrete-choice experiment; **HCPs** = healthcare professionals; **IV** = intravenous; **MAR** = maximum acceptable risk; **MRD** = measurable residual disease; **PFS** = progression-free survival; **TLS** = tumour lysis syndrome.

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This review summarises a recent publication of data from a discrete-choice study conducted by Ravelo et al.,[1] which provides insight into treatment factors adults with chronic lymphocytic leukaemia (CLL) consider important. Past research has shown efficacy as the most important factor, yet qualitative interview participants in this study also identified treatment duration as an important factor in their decision when choosing a CLL therapy.[2] This finding was confirmed by the quantitative preference study, which revealed a preference for fixed-duration therapies over treat-to-progression regardless of the timeframe (6 or 12 months).[2] These findings will help HCPs work with patients individually to choose the best treatment.[1,2] The data were presented in part at the 65th American Society of Hematology Annual Meeting, held last December in San Diego, California.[2] Abbvie Pty Ltd sponsored this review.

Background

Chemoimmunotherapy (CIT) has been the cornerstone of first-line treatment for CLL, the most prevalent form of adult leukaemia, primarily affecting older populations.[3,4] However, it has known toxicities, making it less tolerable for older adults and is proven to be ineffective for patients with high-risk biomarkers.[3,4]

Over the past eight years, the therapeutic landscape for CLL has evolved with the introduction of novel targeted therapies as alternatives to traditional CIT.[3,5–9] These novel agents include Bruton tyrosine kinase inhibitors (BTKIs) such as ibrutinib, acalabrutinib, and zanubrutinib, which can be administered as monotherapies or in combination with obinutuzumab. Additionally, the B-cell lymphoma 2 inhibitor venetoclax has shown promise when used in combination with obinutuzumab or rituximab for a fixed duration or as monotherapy. Current treatment guidelines for patients with CLL meeting the criteria for intervention now incorporate these targeted therapies alongside traditional CIT regimens. BTKIs and CIT are typically administered until disease progression, while venetoclax-based combinations are given for a fixed duration.[3,4,10]

The benefit-risk profiles, treatment durations, and administration routes vary between these novel treatments, requiring a nuanced approach to treatment selection that considers individual patient preferences.[1] Previous patient preference studies in CLL have evaluated some treatment attributes, but there is limited research on preferences for treatment duration as an independent factor.[2,11–14] Thus, the current study sought to quantify the trade-offs patients would consider when choosing between fixed-duration therapies and treat-to-progression approaches.[1,2]

By exploring patient perspectives on treatment duration, this study contributes valuable insights to inform clinical decision-making and enhance patient-centred care in CLL management, potentially leading to improved treatment adherence and outcomes in this complex haematological malignancy.[1,2]

Materials and methods

Patients who were residents of the USA, aged ≥18 years, with a self-reported physician diagnosis of CLL for ≥3 months, and able to read and understand English to provide informed consent were eligible for this study.[1] There were no exclusion criteria.[1] This study was conducted in 2 phases.[1]

Phase 1 qualitative interviews[1,2]

Factors influencing patient treatment preferences were identified through in-depth individual interviews. The semi-structured interview guide included open-ended questions and probes to understand perceptions of fixed-duration treatments compared with treat-to-progression regimens. A list of treatment attributes influencing CLL treatment preference was constructed and informed the development of a web-based discrete-choice experiment (DCE) survey.

Phase 2 quantitative patient preference survey[1,2]

The web-based DCE survey was administered to estimate the trade-offs patients would accept among CLL treatment attributes. There were 12 DCE questions, each offering a choice between two hypothetical treatment profiles defined by seven attributes with varying levels (**Table 1**). Data were analysed using a random-parameters logit model, which provides quantitative estimates of relative preference weights for each treatment attribute level. Estimated preference weights were used to calculate the maximum acceptable risk (MAR) of treatment-related adverse events the average respondent would accept in exchange for changes in treatment duration. The MAR is estimated as the ratio of the relative importance of an improvement in an attribute to the relative importance of a unit change in the level of risk (i.e. tumour lysis syndrome [TLS], atrial fibrillation, or fatigue).

Table 1. Attributes and levels for the DCE.[1,2]

Type of attribute	Technical attribute level	Attribute levels
Efficacy	Percentage of patients achieving PFS at two years confirmed with MRD test[a]	• 90 out of 100 people (90%), confirmed by MRD test
		• 90 out of 100 people (90%) confirmed by routine test
		• 70 out of 100 people (70%), confirmed by MRD test
		• 70 out of 100 people (70%), confirmed by routine test
Process	Mode and frequency of administration	• One oral pill daily at home
		• Two oral pills daily at home
		• IV infusion every four weeks
		• IV infusion every four weeks + one oral pill daily at home
	Duration of treatment	• Fixed – 6 months
		• Fixed – 12 months
		• Until the cancer progresses (gets worse)
Safety	Risk of TLS	• 0 out of 100 people (0%)
		• 1 out of 100 people (1%)
		• 3 out of 100 people (30%)
	Risk of atrial fibrillation	• 0 out of 100 people (0%)
		• 4 out of 100 people (4%)
		• 10 out of 100 people (10%)
	Risk of fatigue	• 0 out of 100 people (0%)
		• 1 out of 100 people (1%)
		• 15 out of 100 people (15%)
		• 35 out of 100 people (35%)

Adapted from Ravelo et al. (2024)[1] and (2023).[2]

[a] In the online survey, the attribute defined by chance of PFS and results confirmed with MRD testing were presented as two distinct attributes. Four combinations exist between the two levels of chance of PFS (70% vs. 90%) and the two testing confirmation levels (routine tests vs. MRD tests).

IV = intravenous; **MRD** = measurable residual disease; **PFS** = progression-free survival; **TLS** = tumour lysis syndrome.

Expert comment

The study design aims to evaluate patient perceptions and preferences toward the major CLL regimens currently available. The DCE and qualitative methodology are appropriate for the nature of the question under consideration. The nature of patient selection does lead to likely selection bias for patients with higher levels of education, health literacy, and English language proficiency.

Results

Phase 1 qualitative interviews[1,2]

Interviews were conducted with 20 adults with a self-reported diagnosis of CLL. The mean age was 59 years, and 55% of participants (n=11) identified as female. The mean time since diagnosis of CLL was 3 years, and 70% of participants (n=14) had received treatment for CLL. A total of 93 treatment attributes were spontaneously reported. All participants (n=20) identified efficacy, safety/side effects, administration mode, and treatment duration as important when considering CLL treatments. When probed, 50% of respondents reported treatment duration as "very important" in their treatment decision. Almost all participants (n=17) preferred treatments with a fixed duration compared with treat-to-progression, assuming each had the same efficacy. The perceived benefits and drawbacks of fixed-duration versus treat-to-progression therapies are summarised in **Table 2**.

Table 2. Participant-reported perceived benefits and drawbacks of fixed-duration versus treat-to-progression therapies (N=20).[2]

	Benefits	Drawbacks
Fixed duration	• Budgeting and anticipating expenses (i.e., being able to plan for medical expenses and not having to pay for treatment repeatedly over an indefinite period) • Convenience (i.e., not having to take a treatment [freedom from medication]) • Being more in control • Not having to refill prescription • Not having to travel for treatment • No short-term side effects when off treatment • Reduced risk of long-term side effects • Getting back to "normal" life	• Concentrated costs (the cost can be very high over a short period) • Side effects might be worse if treatment duration is shorter • Their CLL might worsen or spread if they are not taking medication
Treat-to-progression	• Doing something (i.e., the feeling of comfort gained by taking action and treating their cancer)	• Worry that the medicine may become less effective over time • Cost of treatment • Taking a medicine continuously is a constant reminder of the cancer • Inconvenience (i.e., always taking a medicine) • Getting refills • Following up with the nurse or pharmacy • Continual risk of short- and long-term side effects

Adapted from Ravelo et al. (2023).[2]

CLL = chronic lymphocytic leukaemia.

Phase 2 quantitative patient preference survey[1,2]

A total of 229 adults who met the inclusion criteria completed the DCE survey between April and June 2022. The median age of the sample was 67 years, and nearly 60% of participants (n=136) identified as female. Approximately 60% of the sample (n=138) had been diagnosed for at least five years; 66% (n=152) reported receiving at least one treatment for CLL.

On average, respondents' preferences were ordered as expected, with better levels generally being preferred to worse levels (**Figure 1**). Although respondents preferred fixed-duration treatments to treat-to-progression, they did not differentiate between treatments with a 6- or 12-month duration. This means they were unwilling to trade off worse levels of other attributes to avoid an additional six months of a fixed-duration treatment. A change from treat-to-progression to a fixed, 12-month treatment was approximately 2.2 times more important than reducing the risk of TLS from 3% to 0%. On average, respondents valued having a fixed-duration treatment about the same as minimising the risks of fatigue and atrial fibrillation and having a daily pill instead of IV infusion every four weeks.

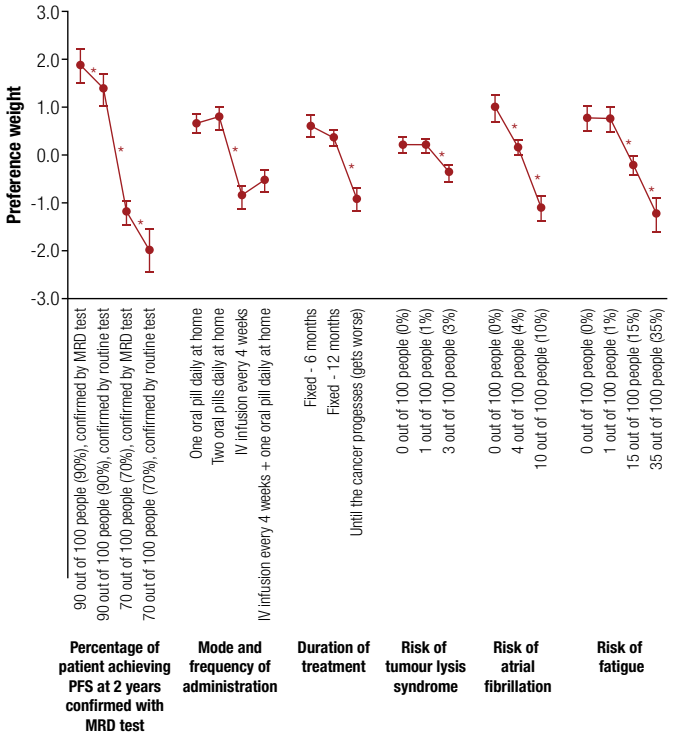

Figure 1. Relative preference weights for treatment attributes (N=229).
Adapted from Ravelo et al. (2024).[1]

*Attribute level changes statistically different from 0 at the 95% CI.

Note: The preference weights measure each attribute level's relative impact on the average respondent's treatment choice. Preference weights are relative and do not have an absolute interpretation. The attribute levels with larger preference weights are preferred to those associated with smaller preference weights. The utility variation caused by a change in the levels of each attribute is represented by the vertical distance between the preference weights for any two levels of that attribute. Larger differences between preference weights indicate that respondents viewed the change as relatively more important. The vertical bars surrounding each mean preference weight denote the 95% CI (computed by the delta method).

CI = confidence interval; **PFS** = progression-free survival; **MRD** = measurable residual disease.

Finally, **Table 3** shows that based on the MAR estimates, respondents were willing to accept the following levels of risks to have a fixed-duration treatment versus treat-to-progression:[1,2]

- >3% increased risk of TLS
- 6–7% increased risk of atrial fibrillation
- 21–26% increased risk of fatigue

Table 3. MAR of treatment side effects in exchange for improvements in CLL treatment characteristics (N=229).[1]

Attribute	From level	To level	MAR of TLS[a]	MAR of atrial fibrillation[a]	MAR of fatigue[a]
			Mean (95% CI)		
Percentage of patients achieving PFS at 2 years confirmed with MRD test	70 out of 100 people (70%), confirmed by routine test	70 out of 100 people (70%), confirmed by MRD test	>3.0	3.8 (1.6–6.0)	12.4 (5.3–19.5)
	70 out of 100 people (70%), confirmed by routine test	90 out of 100 people (90%), confirmed by routine test	>3.0	>10	>35
	70 out of 100 people (70%), confirmed by routine test	90 out of 100 people (90%), confirmed by MRD test	>3.0	>10	>35
	70 out of 100 people (70%), confirmed by MRD test	90 out of 100 people (90%), confirmed by routine test	>3.0	>10	>35
	70 out of 100 people (70%), confirmed by MRD test	90 out of 100 people (90%), confirmed by MRD test	>3.0	>10	>35
	90 out of 100 people (90%), confirmed by routine test	90 out of 100 people (90%), confirmed by MRD test	2.7 (1.1–4.2)	2.4 (0.5–4.3)	8.0 (1.1–14.8)
Mode of frequency of administration	IV infusion every 4 weeks	IV infusion every 4 weeks + 1 oral pill daily at home	N/A[b]	N/A[b]	N/A[b]
	IV infusion every 4 weeks + 1 oral pill daily at home	2 oral pills daily at home	>3.0	6.2 (4.1–8.3)	21.4 (12.1–30.8)
	IV infusion every 4 weeks + 1 oral pill daily at home	1 oral pill daily at home	>3.0	5.7 (3.6–7.9)	19.4 (9.8–29.0)
	IV infusion every 4 weeks	2 oral pills daily at home	>3.0	7.7 (5.7–9.7)	27.7 (18.5–36.9)
	IV infusion every 4 weeks	1 oral pill daily at home	>3.0	7.2 (5.2–9.2)	25.7 (16.3–35.1)
	1 oral pill daily at home	2 oral pills daily at home	N/A[b]	N/A[b]	N/A[b]
Duration of treatment	Until the cancer progresses (gets worse)	Fixed: 12 months	> 3.0	6.2 (4.2–8.1)	21.2 (12.3–30.2)
	Until the cancer progresses (gets worse)	Fixed: 6 months	> 3.0	7.4 (5.3–9.4)	26.2 (17.1–35.2)
	Fixed: 12 months	Fixed: 6 months	N/A[b]	N/A[b]	N/A[b]

Adapted from Ravelo et al. (2024).[1]

[a] MAR estimates outside the range of levels included in the study are noted as greater than the largest difference in levels of risk of TLS, atrial fibrillation, and fatigue: 3%, 10%, and 35%, respectively. CIs are not reported for these estimates. It is possible to estimate a specific value for the MAR outside the range of levels included in the study only by making the strong assumption that the disutility of each unit increase in risk remains constant beyond the greatest level of risk.

[b] The difference between these levels does not have a statistically meaningful impact on the average respondent's preferences. Thus, the MAR for this change cannot be calculated.

CI = confidence interval; **IV** = intravenous; **MAR** = maximum acceptable risk; **MRD** = measurable residual disease; **N/A** = not applicable; **PFS** = progression-free survival; **TLS** = tumour lysis syndrome.

Expert comment

There were several interesting findings from this study. Financial toxicity of therapy and economic predictions was a major consideration for patients. This is not something which necessarily always features prominent in consultation but raises the importance of having these discussions with our patients. Another underappreciated factor from a clinician perspective is the psychological impact of continuous therapy "taking a medicine daily is a continuous reminder of my cancer." This is another important consideration for therapeutic decision making which may not necessarily be raised by patients but clearly is something of concern.

Finally, there was a marked preference overall for fixed duration therapy in the patients surveyed. In general, respondents with CLL placed substantial value on fixed-duration vs continuous therapies, willing to trade off higher rates of fatigue, TLS and atrial fibrillation risk for a treatment-free interval.

Take-home messages

- Respondents placed the most importance on increasing the chance of PFS at two years from 70% to 90% and confirming results with MRD testing instead of routine testing.
- Respondents also preferred daily oral administration over IV infusion every four weeks, treatments with a fixed duration over treat-to-progression therapies, and treatments with a lower risk of side effects; reducing the risk of TLS was the least important relative to changes in the other study attributes.
- Respondents were willing to accept a >3% risk of TLS, the largest risk presented in the survey, in exchange for improvements in treatment duration.
- Confirmation with MRD testing was more important to respondents when the chance of achieving PFS was lower (70%) than higher (90%).
- These insights can aid shared decision-making when selecting treatments for CLL.

Expert's concluding remarks

This study provides useful insights into the views and preferences of patients with CLL regarding the myriad treatment options for the initial treatment of the disease. The strong preference for fixed duration therapy was clear – however, this should be taken in the context of assumed equivalent efficacy. When considering patients with high-risk biologic features such as *TP53* mutation or *IGHV* unmutated status it remains important to highlight the benefits of continuous BTK inhibitor-based therapy in the treatment discussion. However, for patients with *TP53* wild type and *IGHV* mutated CLL where practical, a fixed duration approach is entirely reasonable and may be more likely to align with patient's values and priorities. One caveat to this study is the inevitable selection bias arising from the nature of subject selection. This type of study (requiring a self-reported physician diagnosis of CLL, able to read and write English) will inherently bias findings toward patients with higher levels of education and health literacy. The characteristics of patients included in the study was notable for the median age of respondents (59 years)* and female preponderance – both findings out of keeping for a typical community based CLL population (median age at diagnosis 72 years; male preponderance).

The findings therefore may not necessarily be generalisable to a treatment setting where patients are non-English speaking, have lower health literacy or greater frailty/logistic barriers to accessing treatment. It remains important to have nuanced and (where possible) gradual discussions over several consultations regarding the pros and cons of fixed duration vs continuous therapies. Fortunately, in CLL, serial monitoring often affords ample opportunity to anticipate need to commence therapy.

*This applies to Phase 1 of this study.

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