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ORIGINAL PAPER

Utility elicitation study in the UK general public for late-stage chronic lymphocytic leukaemia

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Abstract
Objectives In the United Kingdom (UK), chronic lymphocytic leukaemia (CLL) makes up 40 % of all leukaemias in patients over 65 years. The study objective was to obtain societal preferences in the UK for "progression-free" and "progressive" states of late-stage CLL, refractory to current first and second line regimens. Preferences were also obtained for selected treatment-related adverse events (AEs).
Methods A utility elicitation study, using the time trade-off (TTO) method, was conducted by face-to-face interviews with 110 subjects for a baseline disease state (before treatment), three primary disease states [progression-free survival (PFS) and treatment responder, PFS and treatment non-responder and disease progression], and 4 AE sub-states (PFS responder with thrombocytopenia, neutropenia, and infection, and PFS non-responder with infection). TTO scores were converted into utility values, and disutilities were calculated for AEs. Visual analogue scale (VAS) scores were obtained.
Results The primary disease state mean TTO utility scores were: baseline: 0.549; PFS response: 0.671; PFS non-response: 0.394; and progression: 0.214. The mean TTO utility (disutility) scores for the AEs were: PFS response with thrombocytopenia, 0.563 (−0.108), neutropenia, 0.508 (−0.163), and infection, 0.476 (−0.195); PFS non-response with infection, 0.333 (−0.061). The VAS results were in line with the TTO results.
Conclusions The utility was higher for the PFS state than baseline, but decreased below baseline in non-response and disease progression states. AEs had an impact on utility within the PFS response state. The severe infection AE had a greater impact on utilities for the responding to treatment state compared to the non-responder state.

Keywords Chronic lymphocytic leukaemia · Utility study · Quality of life study · Time trade-off

JEL Classification I18 · I19

Introduction

Chronic lymphocytic leukaemia (CLL) is the most common type of leukaemia [1], with an incidence rate of approximately 3,000 new cases per year in the United Kingdom (UK) [2]. A recent study reported 5- and 10-year absolute survival from diagnosis as 60.2 % and 34.8 % respectively [3]. Patients with CLL tend to be elderly, with a median age at diagnosis of 72 years, although younger patients are also being diagnosed with increasing frequency [4]. At an early stage of the disease, symptoms are minor and "watchful waiting" is the preferred form of treatment. An indication that the disease has advanced to late-stage CLL is an increased frequency of infections, a common complication of the disease as the immune system becomes severely compromised [5, 6]. Patients with high-risk, late-stage disease may also suffer from disease-related anaemia

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or thrombocytopenia [5]. Subjective symptoms in late-stage CLL include feeling tired, unwell or breathless, bruising and bleeding easily, unintentional weight loss or severe sweating [5, 6]. There is a significant impact on patient quality of life (QoL) associated with the symptoms of CLL due to its impact on disability, fatigue, reduced emotional wellbeing and a fear of death [7, 8].

Current first and second line treatment options with demonstrated efficacy in late-stage CLL include chemoimmunotherapy such as with rituximab, alongside combination chemotherapy with fludarabine and cyclophosphamide [9, 10] or monotherapy with alemtuzumab [9]. However, patients with fludarabine-refractory CLL who are also either refractory to, or unsuitable for, treatment with alemtuzumab have limited treatment options and a poor prognosis [11].

Ofatumumab is a new treatment option that offers a novel approach to refractory CLL treatment as the mode of action differs from rituximab and alemtuzumab [12, 13, 14]. Another novel drug in development for CLL is lumiliximab, although this is not indicated for treatment of fludarabine-refractory patients [15].

The main goal of the drug therapies used in late-stage CLL is to treat symptoms, control the progression of disease, extend survival and, critically, to optimise the health-related quality of life (HRQoL) for the patient. In the UK and elsewhere, health technology assessment (HTA) bodies require patient outcomes such as HRQoL to be measured and incorporated within quality-adjusted life years (QALYs) in order to evaluate the incremental effectiveness and cost-effectiveness of new interventions [16]. For QALY estimation, HRQoL is measured as utility values that represent preferences for disease states. However, the published literature regarding the utility values associated with late-stage CLL is currently very limited [7, 29]. Therefore, the purpose of the current study was to determine the utility values associated with disease states for late-stage CLL, refractory to first and second line treatments used in practice (i.e. fludarabine- and alemtuzumab-containing regimens) designed for use in economic models of the cost-effectiveness of novel treatments for this condition.

Methods

Study design

A UK cross-sectional study was conducted in the general public to elicit utility and disutility values for eight disease states relating to late-stage CLL patients refractory to first and second line treatment. In line with the National Institute for Health and Clinical Excellence (NICE) [16] and the Scottish Medicines Consortium (SMC) [17] preferences, the time trade-off (TTO) approach, a technique used widely for generating utilities required for cost-utility analyses, was used to elicit the utility values. This approach has been used previously in cancer studies and is advantageous in that it is relatively easy for the general public to understand [16, 18, 19]. There are two major steps in any direct utility elicitation study. The first is to design disease state descriptions or 'vignettes', and the second step is to perform the valuation exercise in order to determine preferences and quantify utilities for the disease states. The disease state descriptions were valued from the societal perspective on the principle of equity in order to improve the ability to use the resulting QALY outcomes to make comparisons with other diseases and reduce the potential bias observed with the patient perspective, who may have adjusted to their condition. In addition, the general public perspective recognised by UK HTA bodies as relevant for the UK decision-making framework, in which the National Health Service (NHS) pays for regulatory approved treatments but is itself funded by general public taxpayer revenues and not directly by the patients themselves, was adopted [16].

The valuation exercise consisted of interviews with 110 members of the UK adult population that were conducted across seven geographical locations (Scotland, London, South East, South West, Midlands, North East and North West) to ensure a broad demographic sample.

Development of disease state descriptions

The content of the disease state descriptions (vignettes) of late-stage CLL was compiled from a review of the clinical literature to establish the HRQoL impact of CLL and treatment adverse events (AEs) [6, 8, 11, 20–22]. The vignettes were designed to reflect an 'average' patient aged 70 years with late-stage CLL, and the contextual framework for each vignette encompassed the impact on HRQoL in association with the five domains of the generic European Quality of Life-5 Dimensions (EQ-5D) descriptive system (i.e. the anchor state was designed to account for the impact of the baseline CLL condition on each of the EQ-5D domains of mobility, self-care, usual activities, pain and anxiety/depression, and then each disease state would include a description of the impact of the specific state on one or more of these domains) [23]. A brief introduction to CLL was also designed to provide a background for the respondent who was assumed to have no prior experience or understanding of the disease or the exercise.

The disease state descriptions were validated through in-depth interviews with three UK-based clinical experts for accurate representation of the clinical descriptors. Although it would be ideal to have direct CLL patient input, this was not possible due to CLL not being common and difficulties identifying enough late stage patients who

were well enough and able to provide appropriate validation. In the absence of direct patient input, use of the EQ-5D domains helps provide the clinicians with a clear framework for validating the descriptors in each disease state. Ten pilot interviews were conducted with members of the UK general public to ensure the disease states were understandable and that the TTO exercise could be performed appropriately. Minor amendments to the descriptions and process were made after these pilots.

The selection of an appropriate number of disease states for the utility elicitation exercise is a balance between comprehensiveness and managing responder fatigue, and also the need to reflect health states in an economic model. Based on these criteria, eight disease states were developed—these were an anchor disease state, three primary disease states that correspond to disease states often used in health economic models in cancer and four sub-states incorporating potential AEs associated with the disease or treatment. Eight disease states were felt to be the maximum that each respondent could manage in order to reliably complete the visual analogue scale (VAS) and TTO exercises, and so a limit to four AE disease states (covering three AEs) was made to keep within this cap whilst still ensuring the key late stage CLL AEs were included.

The anchor disease state describes the patient prior to receiving a new treatment, whilst the three primary disease states cover potential outcomes of the new treatment, i.e. a responder to treatment whilst experiencing progression-free survival (PFS) (termed "PFS responder", state 1), a non-responder to treatment with PFS (PFS non-responder, state 5), and disease progression (state 7). In order to explore the disutilities associated with AEs, the PFS responder state was divided into three sub-states incorporating thrombocytopenia, neutropenia without infection, and severe infection. The sub-states were chosen according to the most frequent severe AEs recorded in clinical trials for ofatumumab, defined as grade 3+ by the National Cancer Institute—Common Terminology Criteria for Adverse Events (NCI-CTCAE) [24]. A single adverse event, severe infection, was chosen for assessment of the impact of an AE for the PFS non-responder state as compared to the same AE in the PFS responder state. This AE was selected as it was considered likely to have the greatest impact on HRQoL so providing a better basis for evaluating whether being in a responder or non-responder disease state impacts on AE disutility. The final descriptions of the anchor and disease states are provided in Table 1.

Utility elicitation

Utility elicitation used the TTO method, supported by use of a vertical VAS. The VAS exercise was conducted as a 'warm up' technique to allow the respondent to become familiar with the disease states and the rating concept. This technique requires the respondent to rate each disease state, along with their own health, on a scale of 0 (death) to 100 (full health). VAS was included for a quick assessment of respondent understanding of the exercise, as well as to generate values useful for comparison with those from the TTO. VAS is considered to be a valid measurement tool [25] to use alongside TTO.

Each respondent provided a valuation using TTO or VAS for all the disease states, which was considered feasible with eight states to value. For the TTO exercise, a 10-year time frame was used with the respondent offered more or less time in 'Full Health' compared to 10 years in the disease state until a point of indifference was reached (with fine tuning in months and days). As an example of this procedure, after offering 10 years in full health, the respondent would be offered 1 year in full health versus 10 years in the disease state followed by death, and then 9 years in full health versus 10 years in the disease state and then 2 years in full health versus 10 years in the disease state, 8 years in full health versus 10 years in the disease state, 3 years in full health versus 10 years in the disease state and so on until the respondent accepts the trade-off. Once the point of indifference was reached in 'years' the TTO would be performed to find the months and days between the years in full health that were rejected and the years accepted to identify more precisely the point of indifference. The process only allowed for utilities between 0 and 1 to be generated (i.e. negative utility values were not possible). A 10-year time frame was selected in order to compare the results to a previous utility study, conducted on an earlier stage of CLL [26]. A 10-year time frame is the standard period used for a meaningful TTO exercise [27]; people have more trouble performing the trade-off when much shorter or longer time frames are used. After the anchor state, the primary disease states were presented to the respondents in logical order of worsening health i.e. state 1, 5 and then 7. Each of the relevant AE sub-states were introduced after state 1 and 5, with states 2, 3 and 4 introduced in random order to minimize responder bias.

Respondent recruitment

The objective was to achieve a sample size of at least 100 respondents, which we used as a rule of thumb for the minimum number of general public respondents to achieve a representative cross-sectional sample of society. Recruitment from the seven major geographical regions was in accordance with the IPSOS-MORI general population panel statistics to encourage a broad representation of the UK general public, which is necessary for a societal perspective to be legitimate. Potential respondents

Table 1 Descriptions of the background, anchor and disease states for the visual analogue scale (VAS) and time trade-off (TTO) exercises

State	Description[a]

Background to late stage CLL (female as an example)	Summary of the disease (CLL) from diagnosis to treatment of advanced stage disease, and brief introduction to the exercise:
	• Joan is 70 years old and has a chronic type of leukaemia called chronic lymphocyte leukaemia. This is a cancer that affects the blood and cannot be cured. The disease does not require treatment until it is at an advanced stage
	• For 5 years, Joan had no symptoms and she didn't require treatment. Then her blood condition began to get worse and she started to develop the following symptoms:
	  • night sweats (severe sweats that wake her in the early hours of the morning and are sufficient to wet night clothes and bed sheets)
	  • being very tired all of the time
	  • weight loss and loss of appetite
	  • swollen glands around the neck and under the arms
	  • chest infections and sore throats
	• Joan was able to look after herself (washing and dressing) and do gentle housework. However, Joan is only able to walk a short distance down the street
	• The symptoms meant that the disease is now at an advanced stage so Joan has received her first course of treatment
	• To start with, the treatment was successful and she experienced a time without any symptoms. However, after the disease returned, Joan required another course of treatment. With each course of treatment, it has become harder to relieve the symptoms

Anchor disease state for late stage CLL	Describes a patient prior to treatment with the next line of treatment, having already received one or two lines of treatment (the nature of which was not described): • Joan has had more than one course of treatment. It is less than a year after the last treatment and Joan is experiencing the symptoms again. As well as the symptoms, Joan now has infections regularly, and is constantly tired and has low energy • The doctor wants to try a new treatment • Joan is about to receive the new course of treatment. She will go to the hospital once a week, for 7 weeks to receive a drug through a drip into her arm. The drip is inserted by a nurse and stays in for about 4 hours. After this, Joan can go home. After 7 weeks, Joan only needs to receive the drug by a drip once every 4 weeks, for 4 months • She does not feel well but is still able to look after herself and do gentle housework. Joan feels able to walk short distances
Disease State 1:Progression Free Survial and responding to treatment: "PFS responder"	• Imagine you are Joan • It is now **6 weeks since** the start of treatment. Joan's symptoms started to **improve** 3 weeks ago. The **treatment is working** and her blood condition is improving • Joan is occasionally tired and has minor infections from time to time, but **feels better than before** the new treatment started • However, Joan develops a **red rash** all over her body and has a **high temperature** whilst taking the treatment. She is anxious about this but the doctor explains there is **nothing to worry about** • Overall, Joan **is able to** look after herself, perform other daily activities including housework and comfortably walk down the street. Joan knows the cancer will get worse again but **is able to** make plans for the next 12 months, including having a holiday abroad
Disease State 2: PFS responder + AE: thrombocytopenia	• Imagine you are Joan and the treatment is currently successful • Joan is **still receiving** treatment. The treatment is **working** and Joan's **symptoms have improved** • While Joan is receiving the treatment, she also suffers from **nose bleeds** which may be due to the treatment. As a result, Joan takes a lot **longer to recover** each time she receives the treatment • Due to the **nose bleeds** Joan has to spend half a day in hospital having a **blood transfusion**. This works for a while but the nose bleeds come back so she has to receive **further transfusions** once a week for the **first 2 months** of treatment • As before, Joan **is able to** look after herself, perform daily activities and walk comfortably. However, the transfusions make it difficult for Joan to carry on as before with her usual activities because of the **frequent** trips to hospital
Disease State 3:PFS responder + AE: neutropenia (without infection)	• Imagine you are Joan and the treatment is currently successful • Joan is **still receiving** treatment. The treatment is **working** and her **symptoms have improved** • While Joan receives the new treatment, she also suffers from a worsening **sore throat and fevers** which may be due to the treatment she is receiving • Joan is at risk of developing an ear or chest infection, which if untreated, could lead to **blood poisoning** (sepsis) • Joan is fearful of developing blood poisoning and dying, and worries about leaving the house in case she picks up an infection that may lead to blood poisoning • The district nurse gives Joan two **injections at home** twice a week to help with this side effect. Joan has weekly check-ups with the nurse to make sure the condition doesn't develop into an infection or blood poisoning • As before, Joan **is able to** look after herself, perform daily activities and walk comfortably. However, Joan may be **tired**, **restricted** in her usual activities and **scared** of getting blood poisoning It takes Joan **longer to recover** each time she receives treatment for her leukaemia

Table 1 continued

State	Description[a]
Disease State 4: PFS responder + AE: severe infection	• Imagine you are Joan and the treatment is currently successful • Joan is **still receiving** treatment. The treatment is **working** and her **symptoms have improved** • While Joan is receiving the new treatment, she suffers from a worsening **sore throat and fevers** and also develops a **cough** and a **sharp, stabbing chest pain** • The doctor diagnoses pneumonia which causes Joan some anxiety, as it could lead to **blood poisoning** (sepsis). Joan is fearful of developing blood poisoning and dying • Joan is admitted to hospital to be treated with **antibiotic injections** for a couple of days. She recovers in bed but soon starts to feel a bit better • After the course of antibiotics is finished Joan is still quite **tired**, **frail** and **needs help with the housework and other usual activities**. It takes two weeks for Joan to recover from the pneumonia and then she is able to look after herself, perform daily activities and walk comfortably (as before). It takes Joan **longer to recover** each time she receives treatment for her leukaemia
Disease State 5: Progression Free Survial and not responding to treatment: "PFS, non-responder"	• Imagine you are Joan • It is now **6 weeks since** the start of treatment.Joan's symptoms **have not improved** but are **not getting any worse**. This means she has **not responded** to treatment but her cancer has **stopped** getting worse • Joan feels **weaker than before** the new treatment started and finds it more difficult to recover each time she goes into hospital to receive the drug treatment for leukaemia • Joan **continues** to have the symptoms of the disease (night sweats, extreme tiredness, weight-loss, loss of appetite, swollen glands and frequent infections) • Joan also develops a **rash** and a **high temperature** whilst taking the treatment. She is anxious about these side effects but the doctor explains that there is **nothing to worry about** • At the times when the symptoms are not too bad, Joan **can** look after herself, perform some daily activities including gentle housework, and go for a short walk • Joan worries about how long she will live because the treatment has **not really worked**. She experiences fear of dying • Joan knows the disease will **get worse again very soon** and there are **not many** other treatment options. She wonders whether to carry on with the treatment
Disease State 6 PFS, non-responder + AE: severe infection	• Imagine you are Joan and the treatment is not currently successful • Joan is **still receiving** treatment. The treatment has **not** worked and her symptoms have **not improved** • While Joan is receiving the new treatment, she suffers from a worsening **sore throat and fevers** and also develops a **cough** and a **sharp, stabbing chest pain** • The doctor diagnoses pneumonia which causes Joan some anxiety, as it could lead to **blood poisoning** (called sepsis). Joan is fearful of developing blood poisoning and dying • Joan is admitted to hospital to be treated with **antibiotic injections** for a couple of days. She recovers in bed but soon starts to feel a bit better • Joan is **weaker** than before treatment but able to look after herself, perform **some** daily activities and go for short walks. After Joan is allowed to go home from hospital, she is **frail** and **needs help** with daily activities, including the housework • It takes Joan three weeks to recover from the pneumonia
Disease State 7: Disease progression	• Imagine you are Joan • Joan has **finished** receiving the new course of treatment. She is now **not** being actively treated for her cancer and so no longer suffers from any of the side effects of the treatment • The disease gets **worse again** and Joan experiences all the symptoms of the cancer: swollen glands, night sweats, extreme tiredness, losing weight, maybe getting an infection and she doesn't feel like eating • She bruises easily and gets occasional nose bleeds or bleeding gums. These symptoms are **more severe** than before • Joan now gets **supportive care**, such as blood transfusions and antibiotics to try and relieve the symptoms • Joan feels **thinner**, **weaker** and **frailer** than before the new course of treatment. Joan suffers **pain**, catches **more serious infections** and needs **regular blood transfusions**. The **extreme tiredness** doesn't seem to go away at all • Joan is able to look after herself but **cannot** do her daily activities. Joan **can no longer** walk a short distance down the street. Joan knows she will not live very long and has some **fear** of dying She is **concerned** about being dependent on others and about how her death may affect them

AE Adverse events

[a] The primary disease states are in bold. The sub-states relating to adverse events are disease states 2–4 and 6. The background was provided entirely to increase the participant's understanding of CLL and was not part of the assessment

completed a 13-item screening questionnaire to assess their eligibility for the study and to capture demographic information for sub-group analyses. Exclusion criteria at screening included: participation in market research in the previous 6 months; self or household member employed in market research or the pharmaceutical industry (or related enterprises); younger than 18 years of age. Pilot interviews performed in 10 respondents were not used in the final analysis due to subsequent modifications to wording in the disease state descriptions. In total, interviews were conducted with 110 members of the UK adult population during November and December 2009.

Conduct of interviews

Interviews were conducted by trained and experienced interviewers, and informed consent was received from respondents. The research was carried out according to good practice in conducting health related surveys in the general public. Prior to interviews, respondents were provided with background material explaining both CLL and the VAS exercise. Interviewees first completed the VAS followed by the main TTO exercise. Broad respondent exclusion criteria from the final dataset were defined for the TTO exercise before commencing interviews. Exclusion of data was at the discretion of the interviewer based on a set of listed criteria covering willingness of subject to engage in the TTO exercise, difficulties understanding the TTO exercise and whether there was notable inconsistency in outcomes from the VAS and TTO exercises that appeared to be related to the respondent understanding or willingness to engage in the exercises.

Interviews were conducted individually and respondents were reassured that there were no correct or incorrect answers. The interviewer recorded any comments were made by the respondent that, in the judgement of the interviewer, was felt may have influenced how they completed the TTO exercise (such as personal experience with CLL, any prior knowledge of disease, their state of health on the day of the interview, attitude towards life/death, or lack of understanding about the exercise).

Analysis of the utility data

Data were entered into Excel spreadsheets using double data entry. Data validation, utility value calculation and statistical analyses were conducted using Stata version 10 statistical software. The validity of elicited utilities was examined by assessing logical consistency across disease states and also across methods of assessment. The VAS 0–100 scores were recalibrated to use 0–1 values. The TTO utility values were calculated using the formula of 'Utility$_i$ = time in full health/time in Disease State$_i$, where $_i$ is the various disease states' and hence produced a utility value between 0 and 1. Disutilities were calculated for the AEs by subtracting the utility score of the corresponding disease state with AE from the utility score of the disease state without the AE. Utility results are presented as mean, standard deviation (SD), median (25, 75 % percentiles) and 95 % confidence intervals. Differences between the anchor state and other disease states were examined using the dependent *t* test. The TTO and VAS utility scores were compared in rank order.

Results

Characteristics of study sample

Of the 110 respondents included in the study, 50 % were male, the majority were in the middle age groups (41 % were aged 31–50 years), mainly married (54 %), and employed full time (45 %) or part time (16 %). Forty-eight percent of respondents earned less than £20,000 per year and only 14 % were earning more than £40,000 per year (Table 2). The characteristics of respondents were generally representative of the UK population, with UK statistics showing that in 2010/2011 there were 28.1 % of the population aged between 35 and 54 years [28], 70.7 % were in full or part time employment [29] and 68 % were married [30] (slightly higher than in our sample).

Respondent participation

No major problems were encountered with the operation of the TTO exercise and the collection of data. In terms of potentially illogical answers or having had previous CLL or related experience that may have influenced their responses, comments were noted by the interviewer for 11 respondents. However, as all respondents appeared to have understood the VAS and TTO exercise, there were no anomalous patterns in the results for these respondents and the study sample was deemed large enough to compensate for random errors, none of the issues raised were felt to have impacted materially on the resulting TTO values. Therefore, none of the respondents of the 110 interviewed or the data they provided were excluded from the final analysis of the TTO and VAS data.

Utility results

The TTO utility scores are summarised in Table 3. The scores for the primary disease states were highest for the disease state reflective of a patient with PFS and responding to treatment (PFS responder), and lowest for the disease progression state. The anchor disease state

Table 2 Characteristics of the public respondents in the TTO/VAS study

Characteristic	Respondent sample *N* (%)
Gender—male	55 (50 %)
Age (years)	
18–30	28 (26 %)
31–50	46 (42 %)
51+	36 (32 %)
Marital status	
Single	39 (35 %)
Married	59 (54 %)
Divorced/separated	12 (11 %)
Employment status[a]	
Full time	49 (45 %)
Part time	17 (16 %)
Retired/student	29 (27 %)
Unemployed	8 (7 %)
Other (e.g. volunteer)	5 (5 %)
Highest education	
Secondary school	63 (57 %)
Graduate	32 (29 %)
College/vocational/other	15 (14 %)
Annual income level[b]	
<£20,000	52 (48 %)
£20,000—£39,000	42 (39 %)
≥£40,000	15 (14 %)

[a] $N = 108$, as two respondents did not provide employment status

[b] $N = 109$, as one respondent did not provide income information

(0.549) scored lower than the PFS responder state (0.671) but higher than the disease state for PFS and not responding to treatment (PFS non-responder) (0.394). The difference in mean utility between the best disease state (PFS responder) and worst disease state (disease progression) was 0.457 (Table 3).

Of the PFS responder and AE disease states, the highest mean disutility value compared to the state without the AE was associated with severe infection (−0.195). This disutility was higher than the disutility value for the state of PFS non-responder and severe infection (−0.061).

There was a statistically significant ($P < 0.001$) increase in TTO score from the anchor state to PFS response (Table 3). A statistically significant ($P < 0.001$) decrease in TTO score was also observed between the anchor state and PFS non-responder states with or without infection, or PFS states with neutropenia, and with infection. Only the PFS responder with thrombocytopenia state showed no statistically significant difference to the anchor disease state ($P = 0.474$).

The ranking of the mean utility and disutility scores for the VAS exercise, as well as the comparison between a responder and non-responder for severe infection, are consistent with those from the TTO method (Table 3). As expected, the participant's own health is much higher than any of the disease states (0.859) (Table 3). The range of values reported for the TTO exercise shows that only in the two worse disease states 6 and 7 (PFS non-response and progression) were any zero values registered, with one in the former and two in the latter, and values of one were recorded for all disease states except the progression state (Fig. 1). The spread of values across most of the disease states was wide but similar, although there were a large proportion of low values for disease states 6 and 7 and a relatively less broad distribution for these disease states (Fig. 1).

Discussion

In the current utility study, the course of treating a patient with late-stage CLL, refractory to, or inappropriate for, first or second line CLL treatments (e.g. in UK clinical practice first and second line treatment usually consists of two or more cycles of a fludarabine-containing regimen and 12 or more doses of an alemtuzumab-containing regimen, respectively) was mapped with three primary disease states and four AE sub-states. An anchor disease state also provided a baseline utility value for the patient prior to receiving late stage treatment.

The study demonstrates the detrimental impact of advanced CLL disease states on utilities as assessed by a general public sample, and the associated impact of treatment related AEs. The measurement of utilities provides data to evaluate QALYs associated with treatments. An interesting finding was whilst there was a lower utility value for the PFS treatment responder relative to PFS treatment non-responder states (utility: 0.333 vs 0.476), the responder status per se appeared to have a greater impact in relation to the underlying disease state (disutility: −0.195 vs −0.061). One explanation for this may be that, as the hypothetical patient is responding to treatment, the respondent placed more attention on the impact of the specific AE, compared to the non-responder state. Another possibility is that floor effects mean that the respondent is unwilling to trade-off more time for the relatively worse disease state from the inclusion of the AE. We did not find other studies that have explored this in the same way so further utility studies in cancer examining the impact of the same AE across different treatment response states would be worthwhile in order to verify our findings.

Overall, the study has produced consistent utility results for both the primary disease states and the adverse event sub-states using TTO and VAS methods. The VAS utility values for all the disease states were low in comparison to

Table 3 TTO values and VAS scores for disease states

Disease states[b]	TTO values ($N = 110$)					VAS scores ($N = 110$)	
	Utility mean (SD)	Median (25 %; 75 %)	95 % Confidence interval[a]	Rank order	AE disutility mean	Utility mean (SD)	Disutility mean
Anchor state	0.549 (0.231)	0.592 (0.45;0.682)	0.506, 0.592	3	n/a	0.505 (0.179)	n/a
DS 1 PFS responder	0.671 (0.236)*	0.7 (0.55;0.85)	0.627, 0.715	1	n/a	0.634 (0.172)	n/a
DS 2 PFS responder + AE: thrombocytopenia	0.563 (0.108)	0.583 (0.4;0.75)	0.516, 0.610	2	−0.108	0.491	−0.143
DS 3 PFS responder + AE: neutropenia, no infection	0.508 (0.163)*	0.492 (0.39;0.69)	0.464, 0.551	4	−0.163	0.463	−0.171
DS 4 PFS responder + AE: severe infection	0.476 (0.195)*	0.484 (0.3;0.65)	0.432, 0.519	5	−0.195	0.442	−0.192
DS 5 PFS non-responder	0.394 (0.219)*	0.392 (0.2;0.55)	0.353, 0.435	6	n/a	0.371 (0.17)	n/a
DS 6 PFS non-responder + AE: Severe infection	0.333 (0.061)*	0.321 (0.175;0.45)	0.294, 0.372	7	−0.061	0.319	−0.052
DS 7 Disease progression	0.214 (0.18)*	0.188 (0.075;0.3)	0.180, 0.247	8	n/a	0.189 (0.126)	n/a
Own health[c]	n/a	n/a	n/a	n/a	n/a	0.859 (0.122)	n/a

* $P < 0.05$ when compared with Anchor state

[a] 95 % confidence intervals (CI) estimated using generalized estimating equation (GEE) regression and standard errors are based on robust standard errors

[b] See Table 1 for definitions of anchor and seven disease states (DS)

[c] $N = 109$ for own disease state as one participant refused to comment on own health

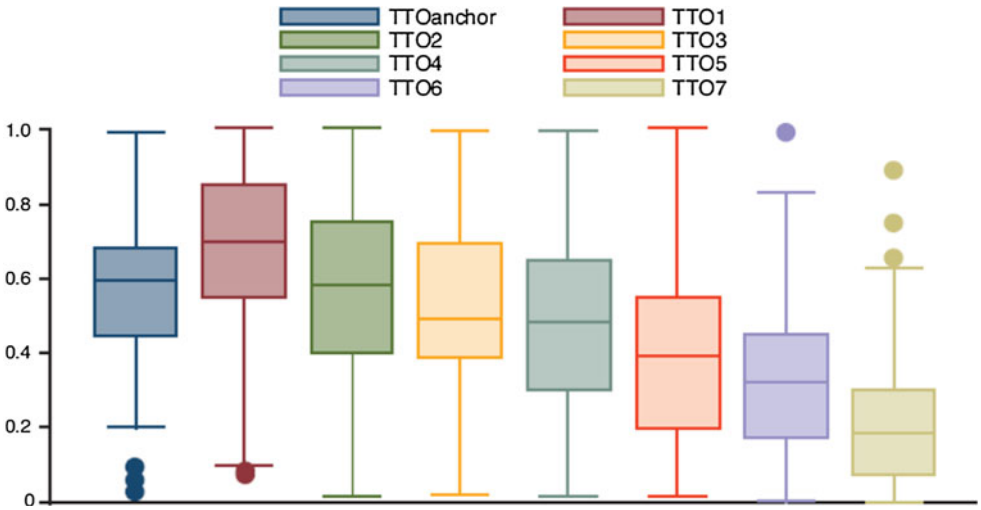

Fig. 1 Box plot of time trade-off (TTO) scores for all diseases. *Boxes* Deviation about the median at the 25 and 75 % percentiles with the max/min plotted as error bars above/below each box

the interview participants' own health, which indicates the respondents understood the exercise. Furthermore, the scores from the TTO exercise were supported by those from the VAS exercise, albeit slightly higher, as would be expected due to the VAS representing a non-choice based approach that does not require trade-offs to be made. A similar difference was also found with a previous utility study on CLL [26].

The findings with the current study are consistent with the findings of a previous UK based utility study that also assessed eight CLL disease states [26]. Both this and our study identified the primary trend to be a decline in the mean utility as patients moved from progression-free to progressive disease states, although the earlier study was set at an earlier treatment stage of CLL. The TTO and VAS scores showed consistent results for both studies, supporting the robust nature of the TTO method.

A further study by Beusterien et al. [32] used the standard gamble (SG) approach to elicit utility values from 89 members of the general public in the UK for CLL patients and found results that have a consistent ordering of outcome but differ in absolute and relative values from our study. This is likely to be related to variation in the valuation approach and differences in disease state definition.

In the study of Beusterien et al. [32], the utility preferences for first-line treatment varied from 0.91 (complete response to first line treatment) to 0.68 (progressive disease), whereas utilities for second- and third-line treatments were 0.71 and 0.65, respectively. The difference in utility values for progressive disease relative to complete response in this study was 0.21, whereas the difference was 0.45 for PFS responder relative to disease progression, and 0.27 relative to PFS non-responder states in our study. In terms of AE dis-utilities, these were similar across the two studies and varied from −0.05 to −0.20 in the Beusterien study, compared to −0.06 to −0.195 in our study, although the specific AEs valued differed across the studies. However, a strength of the direct measurement approach is the ability to elicit values for specific AEs so this consistency of outcome represents an interesting and reassuring finding regarding the reliability of the values we have estimated.

In a study in a similar cancer—Non Hodgkins Lymphoma treated with CHOP (cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone)—a utility of 0.78 for patients in remission at 6 months and no remission at 0.573 using the European Quality of Life (EuroQoL) was estimated [33]. Therefore, the results in our current study are consistent with the above findings, demonstrating the plausibility of the utility elicitation methods used and consequent reliability of the reported results.

There are limitations to the TTO technique, including potential biases due to the discounting effect of time, scale compatibility (where interview participants place more weight on time than on disease state) and loss aversion [34]. Some authors have raised doubts over whether willingness to trade lifetime for improved health reveals true preferences and the stability of the currency of time [35]. There is also a concern over the use of vignettes since they are not based directly on data from trials or other clinical studies, and thus may not accurately reflect the evidence [31]. The vignette descriptions used in the current study were based on a Pubmed literature review of relevant studies in CLL and further validated by experienced clinicians. We felt that this process, as well as using the EQ-5D domains as a framework for the development of the descriptions and clinical validation, led to plausible and unbiased disease states. However, the study would have benefited from direct patient input to further validate the descriptions, but this was not possible due to the practicalities of recruitment of sufficient patients.

To reduce bias wherever possible, the current study used a technique applied previously in TTO studies [36] whereby the interviewer switches between short durations and long durations of full health in comparison to the 10 years in the disease state. In addition, the first three AEs were rotated and the number of interviewers conducting the exercise was limited to minimise interviewer bias. However, even with these methods, some bias may have been introduced by conducting the VAS exercise before the TTO exercise, and by non-randomisation of the other disease states. Participants may have valued the disease states differently once they have seen all the disease states, although this was not found with the comparisons in a previous study [26]. Furthermore, the benefits of 'warming up' the participants with the simple VAS scale to familiarise them with the disease states, prior to TTO, probably outweighs the disadvantages of any potential presentation bias.

A further issue was that the approach used did not allow for negative utilities for any of the disease states to be generated. Negative utilities are somewhat difficult to interpret as they are not bounded (i.e. by 0–1). The implication is that if respondents would have given negative scores if they had been allowed then the mean values for the worst disease states (e.g. disease progression and PFS non-responder with severe infection) would have been lower. On this basis, if the values from our study are applied in an economic model for a treatment that reduces time in disease progression, the utility benefits may be underestimated. However, not including negative utilities appears consistent with the other direct measurement utility studies in CLL.

Finally, we have used a vignette approach with direct TTO measurement of preferences for the disease state. The preferred method of UK Health Technology Assessment bodies in the UK, such as NICE, is to use results generated via a generic utility instrument, ideally the EQ-5D [37]. Whilst there is a higher risk of bias associated with vignette descriptions [38], the advantage and the main reason for the use of this approach in our study was to facilitate the inclusion of direct valuation of specific AEs associated with late stage CLL treatment. This is valuable for using the utility results in economic models of new treatments for refractory late stage CLL to cover both the disease states and main AEs of treatments. In addition, we attempted to base the descriptions on the EQ-5D domains and by using the TTO rather than SG methods in a public sample to mirror the valuation method used in generating the valuation algorithm of the EQ-5D.

Conclusion

This study found that, from a societal perspective and using TTO valuation methodology, the highest mean utility score in late stage CLL was for the disease state corresponding to PFS and responding to treatment without treatment-related AEs. The lowest mean utility score was seen following the final line of treatment for the state associated with progressive disease. However, for the PFS + AE states other

than one for thrombocytopenia (state 2), a lower utility score was estimated compared to the pre-therapy health state. These findings are broadly consistent with expectations and the findings of other published utility studies in the same or similar disease areas. Therefore, the results are reliable and can be used to meet HTA requirements for demonstrating the utility and associated HRQoL impact of late-stage CLL and treatment related AEs. They can also be used to support the assessment of QALY outcomes in economic models of late stage CLL for healthcare decision making.

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