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Patient, physician, and general population preferences for treatment characteristics in relapsed or refractory chronic lymphocytic leukemia: A conjoint analysis

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ABSTRACT

Due to the disease heterogeneity, treatments for chronic lymphocytic leukemia (CLL) have differed with respect to efficacy and toxicity. Limited options have also been available regarding modalities of administration. Our study objective was to estimate preferences for treatment characteristics (or "attributes") in relapsed/refractory (r/r) CLL. Patients, physicians (hematologists/oncologists), and members from the general population from Germany and Sweden completed a conjoint analysis comprising six CLL treatment attributes: (i) overall survival (OS), (ii) progression-free survival (PFS), (iii) fatigue, (iv) nausea, (v) risk of serious infections, and (vi) treatment administration (each described in three levels). We estimated the relative importance of each attribute by fitting a hierarchical Bayesian model. A total of 190 German and 121 Swedish individuals participated. In the pooled sample, OS was the most important attribute (36%), followed by risk of serious infection (21%), treatment administration (13%), fatigue (12%), PFS (11%), and nausea (7%). Treatment administration was more important to patients (all $p < 0.004$), OS was more important to physicians (all $p < 0.001$), and risk of serious infections was more important to the general population than to physicians ($p < 0.001$). Our results could be helpful to align therapeutic decision-making in r/r CLL with patient preferences to improve care satisfaction and treatment compliance.

1. Introduction

Chronic lymphocytic leukemia (CLL) is a cancer characterized by the progressive accumulation of monoclonal B lymphocytes in blood, bone marrow, and other lymphatic tissues, resulting in leukocytosis, hepatosplenomegaly, lymphadenopathy, and bone marrow failure [1]. CLL is designated a rare disease, with an estimated age-adjusted incidence in the UK and US of 4.2 per 100,000 per year, but rates vary markedly by gender and ethnicity. Median age at CLL diagnosis is 72 years and survival ranges from months to several decades [2–4].

Due to the clinical heterogeneity of the disease, and the advanced age of those affected, historically, no universal treatment algorithm has been applicable to all patients with CLL [4,5]. Treatment options have included alkylating agents, anthracyclines, purine analogues, and monoclonal antibodies. However, a number of novel modalities recently licensed and currently in trial are expected to improve patient outcomes across a spectrum of CLL patients. The choice of therapy will continue to be based on a number of factors including severity of disease, patients' age and fitness, and the presence of comorbidities [1,2,4–8]. For patients who have relapsed/refractory (r/r) CLL, duration of response to prior therapy, cytogenetic status, age, stage, and tolerability are key considerations.

From the patient's perspective, in addition to weighing potential benefits and risks, other treatment aspects may be of importance, such as impact on social life, work, and other activities of daily living

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[9]. An increased understanding of patients' preferences for treatment characteristics may as a result help physicians discriminate between available options and potentially enhance overall care satisfaction, increase treatment compliance, and promote patient quality of life [10–13]. Estimates of preferences for CLL treatments could also be helpful to inform health technology assessments (HTAs) and related policy evaluations of CLL therapies.

Previous studies have investigated preferences for interventions of other oncology indications, but little is known of preferences for treatment characteristics (or "attributes") in CLL. The objective of our study was to estimate preferences for treatment attributes in r/r CLL through a conjoint analysis (CA) comprising patients, specialist physicians, and members of the general population from Germany and Sweden.

2. Materials and methods

2.1. The conjoint analysis

CLL treatments are differentiated by a number of attributes, including but not limited to aspects concerning efficacy, safety, and method of administration. Given their preferences, patients, health care practitioners, and other stakeholders may value treatments options differently. However, preferences for treatment attributes are typically not known on a population level and must as a consequence be estimated.

CA is a well-established, evidence-based method used to elicit preferences for product attributes. The method is based on the assumption that a product (e.g., a treatment) can be described by its attributes (e.g., type of administration) and that preferences for a product are based on the levels (e.g., oral pill taken daily at home) of these attributes. To elicit preferences, participants are asked to choose between many different hypothetical products (usually two at a time as a discrete choice) described in terms of the investigated attributes, with different combinations of levels for each product. The responses are then analyzed to estimate the relative importance of the investigated attributes [14].

Good research practice dictates that selection of attributes should be guided by evidence of the potential range of preferences and values that the target population may hold (e.g., from literature and interviews) and the research question [15]. In our study, selection of attributes and levels were informed by (i) a targeted review of the literature (in Medline and Embase), (ii) in-depth interviews with six patients, twelve physicians, and twelve members from the general population, and (iii) in-depth interviews with two CLL expert physicians (one German and one Swedish) (Fig. 1). Each interview lasted for approximately 90 min, and transcripts of the recordings, both in native language and English translations, informed the analysis. A pilot study with five participants (three specialist physicians and two individuals from the general population) was also conducted to further ensure that the content of the survey was accurate and easily interpreted, and that all attributes and levels were relevant and realistic. The pilot survey was followed up with a telephone interview debrief of each participant.

Through these processes, six attributes, each described by three levels, were identified as the primary treatment attributes in r/r CLL (Table 1).

2.2. Participants and procedures

Specialist physicians (hematologists and oncologists) and members of the general population in Germany and Sweden were identified and recruited through online panels managed by Lightspeed AllGlobal, a UK-based specialized fieldwork agency. Patients with CLL were recruited via online panels and patient organizations. We excluded participants <18 years of age, patients with a primary malignant diagnosis other than CLL, German and Swedish physicians who had treated <10 and <5 patients with CLL, respectively, during the last three months (to ensure adequate disease experience), and members of the general population who knew someone with a malignant hematologic disease.

Eligible physicians and members of the general population were invited via email to complete a questionnaire administered on a dedicated study website. Patients were invited via email and phone, and those who were unable to complete the questionnaire online were sent a paper-and-pencil version via post (these responses were subsequently collected via a telephone interview). The study questionnaire consisted of six parts: (i) screening questions, (ii) general information about the study, (iii) information about r/r CLL, (iv) detailed explanation about the CA, (v) 16CA questions, and (vi) background questions concerning the respondent. The questionnaire was initially developed in English and subsequently translated to German and Swedish. Due to the expected sample size of patients and physicians, to retain integrity and ensure confidentiality, we only collected information on age (in categories of ten years), residential community (urban/rural), and marital status from the general population. All participants provided informed consent before completing any study activities.

Each CA question was formulated as a discrete choice between two hypothetical CLL treatments. Fig. 2 shows one of the hypothetical questions as presented to the participants. Physicians and members of the general population were explicitly instructed to complete the CA as if they were a patient. The first CA question constituted a rationality test, where one of the two hypothetical CLL treatments was defined only by the most attractive levels and the other treatment only by the least attractive levels (as identified in the qualitative interviews). Only those who chose the former treatment were included for further analysis. In addition, we also include two identical questions to test response consistency.

The CA was created using Sawtooth Software SSI Web (Sequim, Washington, USA). The CA design, discrete-choice scenarios (combinations of treatment characteristics and levels), and the number of questionnaire versions ($n = 7$) were generated to optimize overall design efficiency in terms of (i) minimal level overlap (each level is shown as few times as possible in each question), (ii) level balance (each level is shown approximately an equal number of times) and (iii) orthogonality (levels may be evaluated independently of other characteristics levels). The average product characteristic level efficiency was 0.88 (ideal design efficiency is 1.00).

2.3. Statistical analysis

We fitted a hierarchical Bayesian (HB) model to the choice data to estimate the average utility part-worths associated with each treatment attribute level. Only main effects (i.e., the independent impact of each attribute) were considered in the model estimation because of the absence of a priori theoretical justifications for interaction effects. The utilities were subsequently used to estimate the mean relative importance of each studied attribute (computed for each patient and then averaged). Attribute importance is a measure of how much influence a specific attribute has on individual choice and expresses the respondent's willingness to trade between attributes. It is calculated as the percentage ratio of the utility difference between the highest and lowest levels within each attribute, respectively, to the sum of differences between the highest and lowest levels across all attributes in total, and range from 0 to 100% per attribute (sum to 100% across all attributes).

We compared estimates across strata using the Mann–Whitney rank sum test. We considered p-values <0.05 to be significant