Cost-effectiveness of First-line Chronic Lymphocytic Leukemia Treatments When Full-dose Fludarabine Is Unsuitable

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ABSTRACT

Purpose: The cost-effectiveness of first-line chronic lymphocytic leukemia treatments was assessed among patients unsuitable for full doses of fludarabine.

Methods: The study's key outcome was the lifetime incremental cost-effectiveness ratio (ICER) (euro/quality-adjusted life-year [QALY] gained) with an annual 3% discounting. A probabilistic Markov model with 3 health states (progression-free, progression, and death) was developed. Survival time was modeled based on age-matched clinical data by using appropriate survival distributions. Each health state was assigned an EuroQoL-5D-3L quality-of-life estimate and Finnish payer costs according to treatment received, and Binet stage of disease; severe adverse events and treatment inconvenience were also included. Six approaches considered the risk and value of key outcomes: cost-effectiveness efficiency frontiers; Bayesian treatment ranking (BTR) rated the lowest ICERs and best QALY gains; the cost-effectiveness acceptability frontier demonstrated optimal treatment; expected value of perfect information; and the cost–benefit assessment (CBA), a type of clinical value analysis, increased the clinical interpretation and appeal of modeled outcomes by including both relative and absolute (impact investment [benefit obtained with a fixed limited budget]) benefit assessments.

Findings: The ICERs compared with chlorambucil varied from €29,334 with obinutuzumab + chlorambucil to €82,159 with ofatumumab + chlorambucil. Based on the BTR of ICERs versus chlorambucil, obinutuzumab + chlorambucil was the most cost-effective with 93% probability; rituximab + chlorambucil was the second most cost-effective (73%); and rituximab + bendamustine was the third most cost-effective (65%). The ICERs of obinutuzumab + chlorambucil were €20,038, €11,556, and €15,586 compared with rituximab + chlorambucil, rituximab + bendamustine, and ofatumumab + chlorambucil. Obinutuzumab + chlorambucil was the most cost-effective treatment, with 54% and 99% probability at €30,000 and €50,000/QALY gained, respectively. The corresponding expected values of perfect information were €1438 and €44 per patient. Based on the BTR of QALYs gained, obinutuzumab + chlorambucil was the most effective, with 100% probability; rituximab + chlorambucil was the second most effective (56%); and rituximab + bendamustine was the third most effective treatment (81%). Results were robust in sensitivity analyses. For obinutuzumab + chlorambucil, the CBA demonstrated the best clinical value–to–cost-effectiveness relation and the longest time progression-free with a limited budget.

Implications: The mean results were sensitive to large changes in time horizon, indirect comparison hazard ratios, survival distributions, and discounting; however, obinutuzumab + chlorambucil provided considerable effectiveness and best value for money among chronic lymphocytic leukemia patients unsuitable to

Accepted for publication February 3, 2016.
http://dx.doi.org/10.1016/j.clinthera.2016.02.005
0149-2918/$ - see front matter

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receive full doses of fludarabine. In this case, CBA concurred with the key outcome of the study. However, the CBA cannot fully substitute the key outcome, and further cost-effectiveness studies with different cancer types are needed to assess the validity of a limited CBA. (*Clin Ther*. 2016;38:889–904) © 2016 The Authors. Published by Elsevier HS Journals, Inc.

Key words: bendamustine, chronic lymphocytic leukemia, economic evaluation, obinutuzumab, ofatumumab, rituximab.

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is the most common type of leukemia, accounting for 25% to 40% of all leukemias.[1,2] The annual incidence of CLL is 2 to 6 per 100,000 population,[1,3] with a preponderance of male subjects over female subjects. CLL is more common in elderly people, with almost one half of the newly diagnosed CLL patients being at least 75 years of age. CLL causes significant humanistic[4–10] and economic[9,11,12] burdens.

Immunochemotherapy with rituximab + fludarabine + cyclophosphamide (RFC) has been the standard first-line treatment for patients with CLL who require and can tolerate intense chemotherapy. However, older patients with comorbidities are often ineligible for RFC.[13] For these patients, chlorambucil monotherapy (Clb) is often used, even though it rarely induces complete responses.[14–16] Currently, combination regimens, including obinutuzumab + chlorambucil (GClb), ofatumumab + chlorambucil (OClb), rituximab + bendamustine (RB), and rituximab + chlorambucil (RClb), are considered because of their efficacy and limited toxicity.

The present study is the first to estimate the cost-effectiveness of all relevant treatments among patients with CLL unsuitable for full-dose fludarabine and, thus, RFC therapy to the best of our knowledge. It is also probably the first to elaborate on the results of a full health economic assessment involving 6 different methods: cost-effectiveness efficiency frontiers; Bayesian treatment ranking (BTR); cost-effectiveness acceptability frontier (CEAF); expected value of perfect information per patient (EVPI); limited cost–benefit assessment (CBA), which is a clinical value analysis; and impact investment analysis (IIA) based on the CBA.

MATERIALS AND METHODS

A decision-analytic modeling approach was used to conduct the cost-effectiveness analysis (CEA) presented here. This CEA meets the Finnish requirements for health economic evaluations,[17] which concurs with most European guidelines.[18–27]

Clb, GClb, OClb, RB, and RClb were compared by using a probabilistic, long-term, Markov transition model (Figure 1) with 3 mutually exclusive key health states in patients with CLL who were unsuitable for RFC. A 1-week model cycle length with life-table method of half-cycle correction[28,29] was applied.

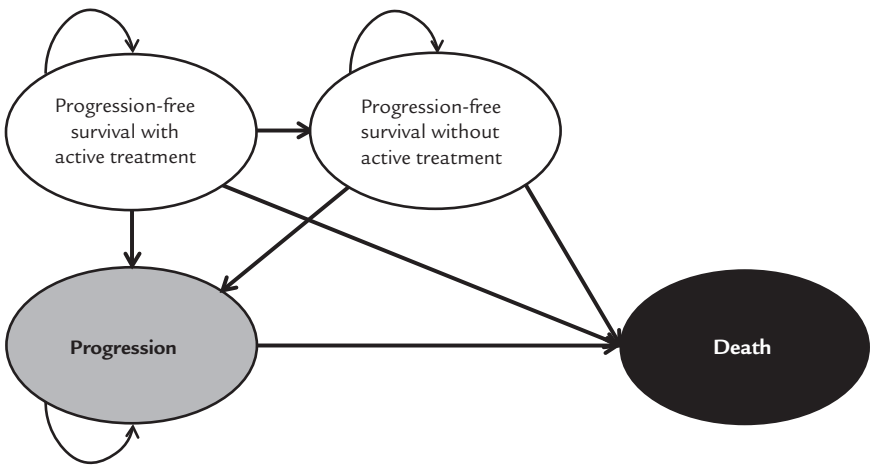

Figure 1. Simplified presentation of the Markov model.