VALUE IN HEALTH ▮ (2018) ▮▮▮–▮▮▮

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A Generic Model for Follicular Lymphoma: Predicting Cost, Life Expectancy, and Quality-Adjusted-Life-Year Using UK Population–Based Observational Data

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ABSTRACT

Objectives: To use real-world data to develop a flexible generic decision model to predict cost, life expectancy, and quality-adjusted life-years (QALYs) for follicular lymphoma (FL) in the general patient population. **Methods:** All patients newly diagnosed with FL in the UK's population-based Haematological Malignancy Research Network (www.hmrn.org) between 2004 and 2011 were followed until 2015 (N = 740). Treatment pathways, QALYs, and costs were incorporated into a discrete event simulation to reflect patient heterogeneity, including age and disease management. Two scenario analyses, based on the latest National Institute for Health and Clinical Excellence (NICE) guidelines (rituximab induction therapy for newly diagnosed asymptomatic patients and rituximab maintenance therapy for patients between treatments), were conducted and their economic impacts were compared to current practice. **Results:** Incidence-based analysis revealed expected average lifetime costs ranging from £6,165 [US$7,709] to £63,864 [US$79,862] per patient, and average life expectancy from 75 days to 17.56 years. Prevalence-based analysis estimated average annual treatment costs of £60–65 million [US$75-80 million], accounting for approximately 10% of the United Kingdom's annual National Health Service budget for hematological cancers as a whole. Assuming that treatment effects reported in trials are applicable to all patient groups, scenario analyses for two recent NICE guidelines demonstrated potential annual cost savings for the United Kingdom that ranged with uptake frequency from £0.6 million to £11 million [US$0.75-2.75 million]. **Conclusions:** Costs, survival, and QALYs associated with FL vary markedly with patient characteristics and disease management. Allowing the production of more realistic outcomes across the patient population as a whole, our model addresses this heterogeneity and is a useful tool with which to evaluate new technologies/treatments to support healthcare decision makers.

Keywords: cost, cost-effectiveness analysis, discrete event simulation, economic evaluation, follicular lymphoma, patient level simulation.

Introduction

Accounting for approximately 20% of all non-Hodgkin lymphomas (NHLs), approximately 1860 patients are newly diagnosed with follicular lymphoma (FL) each year in the United Kingdom [1–3]. FL, the most common of the indolent NHLs, typically follows a remitting relapsing course; initial management ranges from "watch-and-wait (W&W)" (active monitoring/observation) to immediate treatment with chemotherapy/radiotherapy or palliative care. In most cases, therapy is given in response to symptoms, with some patients having several lines of treatment while others remain on W&W. More recently, however, instead of simple W&W, the use of rituximab induction therapy as a strategy to delay the need for chemotherapy/radiotherapy has been recommended and adopted as a treatment option in newly diagnosed asymptomatic patients with advanced stage disease [4]. Although FL is currently incurable, the numbers and combinations of life-prolonging treatments (chemotherapies including novel targeted agents and radiotherapy) is expanding; with individual patients differing widely in their need for, and response to, different treatment regimens the resulting patient pathways are becoming increasingly complex and diverse. This heterogeneity, coupled with the fact that FL in approximately 20% of patients transforms to the more aggressive NHL subtype diffuse large B-cell lymphoma (DLBCL), makes decision making on resource allocation challenging.

This study has ethics approval (REC 04/01/1205/69) from Leeds West Research Ethics Committee. R&D approval from each NHS Trust in the study area and exemption from Section 251 of the Health & Social Care Act (PIAG 1-05(h)/2007). H-I. Wang, A. Smith, E. Aas, E. Roman, S. Crouch, C. Burton, and R. Patmore have no conflicts of interest.

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1098-3015$36.00 – see front matter

https://doi.org/10.1016/j.jval.2018.03.007

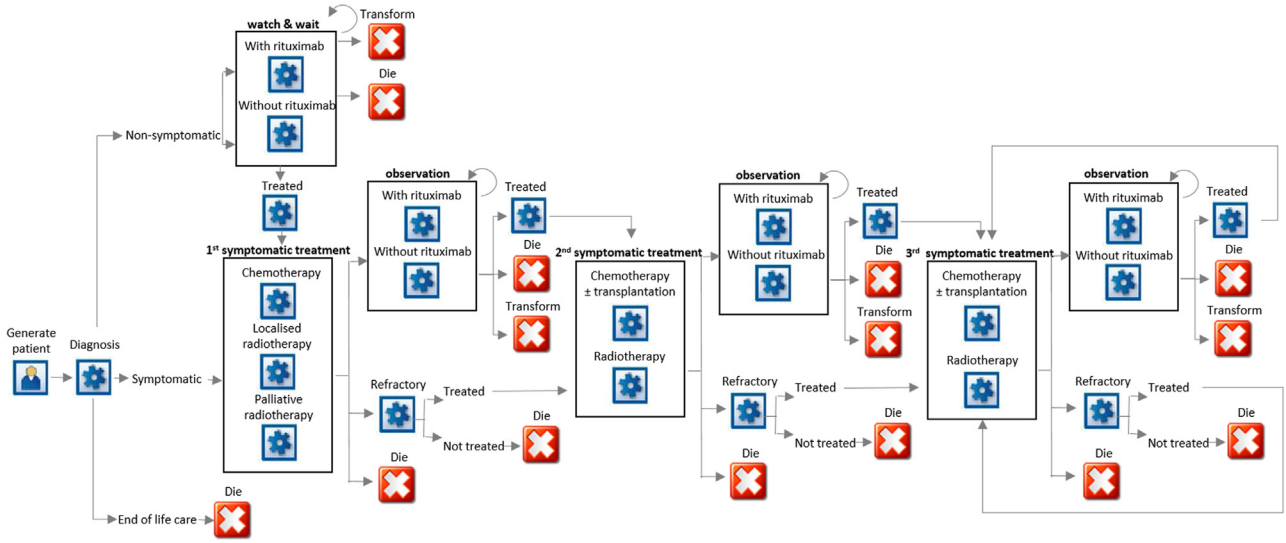

Fig. 1 – Model structure.

In recent years, a number of economic studies have been carried out in FL treatment trials [5–22]. The majority of these have focused on comparing the cost-effectiveness of administering the monoclonal antibody rituximab at particular points along the patient pathway, either in combination with chemotherapy (immunochemotherapy) both as first-line therapy and subsequently for relapsed/refractory disease, or alone (monotherapy) either as frontline in the W&W phase or as maintenance during remission [7–22]. However, the findings from such studies can provide only limited information to policymakers, not only because they relate to selected patients at specific points in time but also because certain groups, such as those treated palliatively and those whose disease transforms to DLBCL, are excluded [7–22].

The overarching aims of the present study were twofold: first, to provide insight into real-world FL treatment costs, survival, and quality-adjusted life-years (QALYs), and second to develop a generic FL model that 1) modelled the whole treatment pathway, rather than being limited to a specific treatment line or agent, 2) reflected real world practice rather than the idealized predefined setting of a randomised controlled trial, 3) predicted medical costs, life expectancy and quality-adjusted life years (QALY) throughout the treatment pathway, and 4) allowed different scenarios to be run, in order to evaluate the impact of changes in disease management on both cost and survival.

Methods

Data Sources

The individual-level data used for constructing the simulation model are from the United Kingdom's Haematological Malignancy Research Network (https://www.HMRN.org), a specialist population-based registry that since 2004 has tracked all patients newly diagnosed with hematological cancers (lymphomas, leukemias, and myelomas) in a catchment population of approximately 3.8 million. Details of the methods underpinning HMRN are described elsewhere [1,23,24]. Key to the present report is the fact that HMRN has Section 251 support under the NHS Act 2006, which allows full-treatment, response, and outcome data to be collected to clinical trial standards regardless of patient consent, as well as "flagging" for death at the national Medical Research Information Service (MRIS) and linkage to nationwide information on Hospital Episode Statistics (HES).

The current study includes all 740 patients 18 years of age or older newly diagnosed with FL (International Classification of Disease for Oncology, 3rd ed.: 9690/3, 9698/3) between September 1, 2004 and August 31, 2011 within HMRN's catchment population. For the purposes of the present analyses, all patients were followed until August 31, 2015, death, or disease transformation to the more aggressive DLBCL. Treatment pathways were mapped according to the management/therapies received. A detailed summary of patient characteristics is presented in Supplementary Table 1.

Model Structure

To reflect real-world treatment strategies, as well as the heterogeneity of patient characteristics, a discrete event simulation (DES) model was constructed using Simul8 software (Simul8 2017 Professional version, Simul8 Corporation, Boston, MA, USA).

Figure 1 shows the model structure, which is based on real patient pathways, clinical experience (RP, CB), and published clinical guidelines [25]. The key input parameters used in the model are listed in Table 1. For more details, please refer to Supplementary Tables 2 and 3.

The model first assigns attributes: age at diagnosis, sex, disease stage, and prognostic index (FLIPI–FL International Prognostic Index [26]) to a simulated patient group based on HMRN's study population distributions. Each patient then moves forward to the next event, with probabilities based both on his or her own characteristics and on his or her event history, rather than fixed-time cycles.

The pathways of all simulated patients are modeled starting from the date of diagnosis, with costs of diagnostic biopsies, scans, electrocardiography (ECG), and echocardiography (ECHO) included. Each patient is then assigned to one of three different treatment options determined by his or her baseline characteristics: W&W (with or without rituximab monotherapy), first-line chemotherapy or radiotherapy, or supportive end-of-life care. Patients initially assigned to W&W can go on to receive first-line chemotherapy and/or radiotherapy when their cancer becomes symptomatic, and at this point in the pathway (first-line) radiotherapy can be localized (stage IA disease) or palliative (symptom control). The disease of patients on W&W may also undergo transformation to the more aggressive, but potentially curable,