PharmacoEconomics (2024) 42:1177–1179
https://doi.org/10.1007/s40273-024-01421-8

COMMENTARY

Using Cure Modelling for Cost Effectiveness in the NICE Technology Appraisal of Polatuzumab Vedotin in Combination for Untreated Diffuse Large B Cell Lymphoma: An External Assessment Group Perspective

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Accepted: 21 July 2024 / Published online: 9 August 2024

1 Introduction

New techniques for survival modelling have been developed, such as cure mixture modelling [1]. These techniques have the potential to improve the accuracy of survival fit estimates and hence increase confidence in the cost-effectiveness results. Mixture cure models assume that there are two distinct subpopulations: the cured population and non-cured population, which are modelled separately.

This type of modelling has not yet been widely used in health economic analyses and more discussion on examples of these models will improve decision making and interpretation of these models. This commentary piece sets out the observations of the Evidence Assessment Group (EAG) on the use of the cure modelling for the technology appraisal submitted to NICE for polatuzumab in combination with rituximab, cyclophosphamide, doxorubicin and prednisolone (R-CHP) for untreated diffuse large B cell lymphoma (DLBCL) in adults (TA874) [2].

2 Cost-Effectiveness Evidence for Polatuzumab for Diffuse Large B Cell Lymphoma

NICE invited the manufacturer of polatuzumab vedotin (brand name Polivy) [Roche] to submit clinical and cost effectiveness evidence of their product for patients with untreated diffuse large B cell lymphoma. The company developed a de novo cohort-based partitioned survival model to estimate the cost-effectiveness of polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin and prednisolone (R-CHP) compared with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) for patients with untreated diffuse large B cell lymphoma. The model contains three mutually exclusive health states: progression free (PF), progressed disease (PD) and death. The proportion of patients in each health state at different time points is based on the progression free survival (PFS) and overall survival (OS) curves from the POLARIX trial [3]. The perspective of the analysis is the National Health Service (NHS) and Personal Social Services (PSS). Costs and QALYs are discounted at 3.5% in the base case, as per the NICE reference case [4]. In the base case, the model has a lifetime horizon of 60 years. Pola+R-CHP and R-CHOP are given for up to six cycles each lasting 21 days. Patients whose disease progresses can commence a new anti-lymphoma treatment.

The proportion of patients transitioning between the health states were predicted by estimating parameter survival models for the PFS and OS curves beyond the trial duration. The company fit mixture cure models to the survival data from the POLARIX trial as the treatment was considered to be a cure in patients who remained in remission after 24 months [5]. For PFS, the generalised gamma distribution was chosen for the base case in both treatment arms. The cure fraction for the generalised gamma was 75% for Pola+R-CHP and 64% for R-CHOP. The generalised gamma distribution was chosen for the base case for OS in both treatment arms. Pola+R-CHP did not show a statistically significant benefit in OS over R-CHOP in the POLARIX trial with a hazard ratio of 0.94 (95% confidence interval

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[CI] 0.65–1.37). For this reason, the OS cure fraction was assumed to be the same as calculated for PFS cure fraction.

The company's base case comparison of polatuzumab vedotin + R-CHP vs R-CHOP produced an incremental cost effectiveness ratio (ICER) of £34,398 per QALY. The cost-effectiveness results presented include a confidential PAS discount price for polatuzumab and the company assumed a 50% discount for rituximab. However, they did not include existing discounts for the other anti-lymphoma therapies in the model. The company presented a series of sensitivity and scenario analyses to test the structural assumptions of the model. The results were sensitive to using alternative models for the survival modelling.

3 ERG Critique of the Cost-Effectiveness Evidence

The ERG notes that there is no statistically significant difference in OS between Pola+R-CHP and R-CHOP (HR 0.94; CI 0.65–1.37) based on presented (immature) trial data at 30 months. However, the company's extrapolation assumed a continued survival benefit for Pola+R-CHP over R-CHOP. We view that that the OS benefit of Pola+R-CHP is highly uncertain. We therefore suggested assuming no long-term survival benefit beyond that observed in the trial data. We assumed that the treatment effect reduces linearly from 30 months to 60 months. We preferred to use the Kaplan Meier data for the trial period (up to 30 months), rather than the fitted parametric curve. We used a generalised gamma extrapolated tail. These changes increased the ICER from £34,306 to £93,705 per QALY.

4 Methodological Issues: Mixture Cure Survival Modelling

Mixture cure models may be appropriate in cases where there is evidence to support the assumption that a proportion of patients may be cured, i.e. a proportion of patients enter long-term remission and have long-term prognosis similar to the general population [1]. Mixture cure models assume that there are two distinct subpopulations: the cured population, which is considered to have the same risk of mortality as the age and sex matched general population; and the subpopulation that remains affected by the disease in question. For the non-cured population, the mortality rate is defined by a selected standard parametric survival curve. The proportion of people in the cured population is known as the 'cure fraction' and is estimated alongside other survival estimates when using a parametric model. The extrapolations for each subpopulation are then combined using the cure fraction to obtain the extrapolations for the whole population.

This appraisal was unusual in that the company demonstrated evidence of a cure for patients by showing that patients who remained in remission (i.e. whose disease has not progressed) after 24 months had similar lifetime survival (albeit slightly lower) than matched age and sex individuals in the general population [5]. The proportion of patients assumed to be 'cured' was estimated to be about 64% for R-CHOP.

As discussed above, the OS benefit for Pola+R-CHP was uncertain. To attempt to include this uncertainty, the ERG assumed that the risk of mortality would be the same after 60 months in both treatment arms. However, this assumption, meant a reduction in mortality for polatuzumab is applied to the whole population, even those whose disease is cured. The NICE Appraisal committee noted that applying a reduction in mortality to the whole population in the context of the mixture-cure model, meant that there appeared to be a reduction in the 'cured' population. It therefore considered this approach to lack clinically plausibility. Further they accepted a benefit in survival for polatuzumab + R-CHP on the basis that a benefit had been demonstrated in PFS and they considered that this benefit was likely to also apply to OS, although it had not been demonstrated within the time limits of the clinical trial.

The ERG suggests that alternative approaches are needed to implement their preferred assumptions which maintain clinical plausibility, such as making changes to the cure fraction for polatuzumab + R-CHP to be equal to that of R-CHOP.

5 Key Learning Points

- Mixture cure models may be appropriate in cases where there is evidence to support the assumption that a proportion of patients may be cured. Ideally this assumption would be validated with observational and clinical evidence.
- Where the mortality of the population is low, there may not be mature data available for overall survival and there may be the need to make assumptions on the cure fraction based on the progression-free survival arm.
- In cases where there is no statistical difference in the treatment effect for overall survival, the treatment benefit in PFS may give an indication of the likely long term benefit for OS, in a population where a proportion may be cured.

6 Conclusion

The primary evidence for this STA process came from the POLARIX trial. The evidence suggests that polatuzumab + R-CHP provides an improvement in PFS for patients with DLBCL compared to R-CHOP. It is not clear if Pola

+ R-CHP increases OS compared with R-CHOP. The economic modelling suggests that polatuzumab is a cost-effective use of NHS resources provided that polatuzumab is offered to the NHS with the agreed confidential patient access scheme.

Declarations

Author contributions All authors contributed to the critical review of the clinical and cost effectiveness evidence and drafting of the EAG report. KC wrote the first draft of this manuscript. All other authors reviewed and approved the final version.

Funding This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Program (project number 135558) [see the NIHR Journals Library website for further information—https://www.journalslibrary.nihr.ac.uk/#/]. The views and opinions expressed are the authors' and do not necessarily reflect those of the HTA Programme, NICE, NIHR, NHS, or the Department of Health. Any errors are the responsibility of the authors. This summary of the ERG report was compiled after NICE issued the Final Appraisal Determination.

Availability of data and materials Not applicable.

Code availability Not applicable.

Conflict of interest All authors (KC, EM, MTT, JS) have no conflicts of interest.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

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