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Evaluating the cost-effectiveness of the addition of rituximab to chemotherapy in the first-line treatment of Follicular Lymphoma patients in the UK

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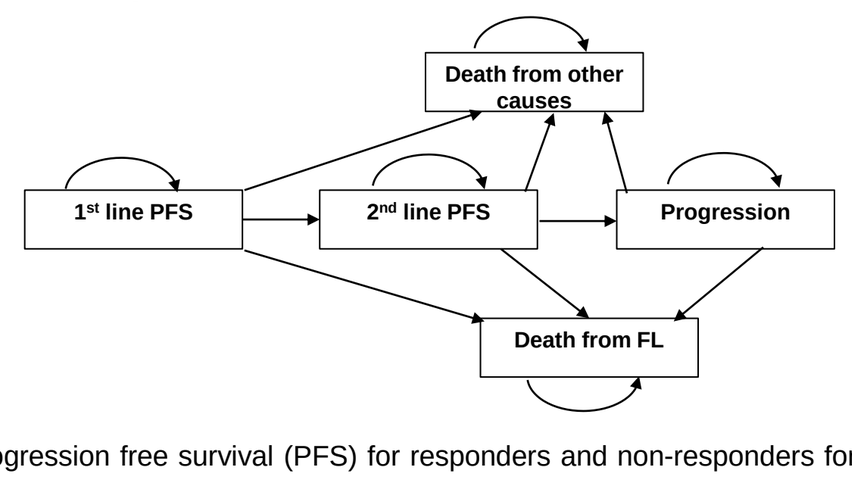
INTRODUCTION

Follicular lymphoma (FL), a clinical subtype of Non-Hodgkin's lymphoma (NHL) , develops slowly and often without symptoms for many years. In 2008, the incidence of FL in England and Wales was 3.4 per 100,000 persons. Over 70% of FLs are diagnosed in persons aged over 60 years, and 85-90% present with advanced disease, which is defined as lymph nodes on both sides of the diaphragm being involved (stage III) or disease is disseminated with one or more extra-lymphatic organs involved (stage IV). Advanced FL is not curable, thus the aim of disease management is to both increase patient life expectancy and to increase patient health-related quality of life. The objective of this study is to assess, from a UK NHS perspective, the cost-effectiveness of the addition of rituximab (R) to selected chemotherapies: CVP (cyclophosphamide, vincristine and prednisolone); CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) and MCP (mitoxantrone, chlorambucil and prednisolone) in the first-line treatment of follicular lymphoma.

METHODS

A patient level simulation model was developed with five mutually exclusive and exhaustive health states (Figure 1): progression free survival on first-line treatment (PFS1); progression free survival on second line treatment (PFS2); progressive disease (PD); death from FL and death from other causes. Patients enter the model in PFS1 and first-line treatment consisted of chemotherapy or R-chemotherapy. Patients relapsing before death move into PFS2 and are assumed to receive second-line treatment dependent on initial treatment and time of relapse. After progression, patients enter the progression state where they reside until death. Patients in PFS1 and PFS2 are subdivided into responders and non-responders using the response rates from the applicable trials,[1,2,3] with responders having on average a better prognosis. Responders to R-chemotherapy in first-line induction were assumed to receive rituximab maintenance for up to 2 years. Separate analyses were undertaken assuming no maintenance for patients who responded to R-chemotherapy in first-line induction (results presented in bracket). Responders in second line (rituximab combination or chemotherapy alone) may receive rituximab maintenance for up to 2 years dependant on the time of relapse.

Figure 1: Simplified schematic of the model structure



The progression free survival (PFS) for responders and non-responders for patients treated with CVP and R-CVP in first-line induction was extracted from an analysis of the M39021 trial.[1] A log-normal distribution was fitted to the Kaplan Meier (KM) data. There was uncertainty regarding the effectiveness of CHOP and MCP with or without rituximab as first-line induction treatment due to the confounding effect of maintenance therapy with interferon or stem cell transplant (SCT) for responders in the main trials.[2,3] Therefore, we used PFS data from the M39021 trial for responders and non responders,[1] but the response rates from the respective trial for CHOP, R-CHOP, MCP and R-MCP. Data from the PRIMA study was used to alter the risk of progression[4] for responders to R-chemotherapy receiving first-line maintenance. A hazard ratio of 0.55 (CI: 0.44 – 0.68) was applied to the rate of progression for responders to R-chemotherapy for the first 42 months.[4] Second line treatments consisted of CHOP, FC or HDT+SCT with or without rituximab. Maintenance therapy was assumed for patients responding to chemotherapy with or without rituximab in second line treatment depending on the time at relapse. Effectiveness data in second line for CHOP and R-CHOP with or without maintenance was taken from the EORTC 20981.[5]

The model horizon was 25 years with costs and benefits discounted at 3.5%. The treatment pathway was defined after discussion with clinical experts and considered the regime received, the time at relapse and age.

Treatment adverse events were included in first-line only. Utility values were extracted from an unpublished UK study.[6] Costs were extracted from official sources (BNF, NHS reference costs) but assumptions were sometimes necessary.

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RESULTS

The Incremental Cost-Effectiveness Ratios (ICERs) for the addition of rituximab to CVP, CHOP and MCP are £14,959, £21,687 and £20,493 per QALY gained respectively when it was assumed that patients responding to first-line induction with R-chemotherapy receive first-line maintenance rituximab for up to 2 years (Table 1). When it was assumed that first-line rituximab maintenance was not used, the ICERs for the addition of rituximab to CVP, CHOP and MCP improved to £7,720, £10,834 and £9,316 per QALY gained respectively.

Table 1: Basecase deterministic cost-effectiveness results

					Probability CE at different WTP	
	Undiscounted LY	**Discounted Cost**	**Discounted QALY**	**ICER**	**20K**	**30K**
CVP	9.86	£30,793	5.99			
R-CVP	12.03 (11.5)	£49,520 (£38,183)	7.25 (6.95)			
Cost per QALY gained				**£14,959 (£7,720)**	**95.6% (100%)**	**100% (100%)**
	Undiscounted LY	**Discounted Cost**	**Discounted QALY**			
CHOP	11.55	£34,983	6.84			
R-CHOP	13.02 (12.4)	£54,134 (£40,708)	7.72 (7.37)			
Cost per QALY gained				**£21,687 (£10,834)**	**36.0% (88.5%)**	**91.5% (95.7%)**
	Undiscounted LY	**Discounted Cost**	**Discounted QALY**			
MCP	11.45	£36,103	6.79			
R-MCP	12.89 (12.35)	£54,079 (£41,370)	7.67 (7.36)			
Cost per QALY				**£20,493 (£9,316)**	**44.9% (92.1%)**	**91.9% (96.7%)**

**Results for the scenario analysis excluding first-line maintenance are presented in brackets*

A range of sensitivity analyses were conducted varying the time horizon, discount rates, the parametric distribution used to model the effectiveness in first-line, the proportion of progression attributable to death, the effect of resistance to rituximab in previously exposed patients, the maximum time a patient can stay in PFS1, health state utility values, changes in the treatment pathway, the effectiveness of therapies used in second line, adverse events, management costs and the impact of first-line maintenance. Sensitivity analyses indicated that the ICER was mostly sensitive to the assumptions about the time horizon (the ICER improved as time horizon increased), the choice of parametric distribution to model the effectiveness in first-line induction (the ICER improved using a Gompertz distribution), the maximum time a patient can remain progression-free (the ICER improved as the time increased), assumptions regarding resistance to rituximab (the ICER deteriorated assuming a lower effectiveness for re-retreatment with rituximab), the modelled treatment pathway and assumptions about the impact of first-line maintenance.

DISCUSSION

There are some limitations relating to the sources of data used in the model for the effectiveness in first- and second-line and the assumed utility values. There is little evidence available regarding the effectiveness of R-CHOP and R-MCP in first-line induction. There is also uncertainty about the effect of salvage treatment in patients previously treated with an anthracycline regimen. Finally, there is uncertainty whether rituximab is as effective in second-line when patients have been previously treated with rituximab.

CONCLUSIONS

The addition of rituximab to CVP, CHOP and MCP is expected to fall below a cost per QALY gained of £25,000 regardless of the assumption on maintenance. Results are not directly comparable across chemotherapies since they are selected in clinical practice with regard to factors including age, performance status and disease aggressiveness.

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