Rituximab Cost Analysis for Maintenance Treatment of Patients With Follicular Lymphoma

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Abstract

Introduction: In patients with refractory or recurrent follicular lymphoma responding to induction therapy with CHOP or rituximab + CHOP, maintenance treatment with rituximab compared to the "observation" option improves both overall survival and progression-free survival.
Objective: Estimate whether maintenance treatment with rituximab is a cost-effective intervention compared to the clinical practice of "observing" its evolution.
Method: Population: the EORTC 20981 clinical trial population. Perspective: Spanish National Health System (direct healthcare costs). Design: Incremental cost-effectiveness analysis, with a transition model between states of health. Main variables: cost of gaining a quality-adjusted life year (QALY), per life year gained (LYG) and per progression-free LYG. Premises of the basic case: Weibull distribution for survival extrapolation, 5 year duration of the benefits of the treatment, time horizon of 10 years, and annual discount rate (costs and benefits) of 3.5%. These premises were modified in the sensitivity analyses.
Results: Deterministic analysis: the cost per QALY gained was €9358, €8493 per LYG, and €5485 per progression-free LYG. Probabilistic and sensitivity analysis: they confirmed the stability of the deterministic analysis results.
Conclusions: According to this model, maintenance treatment with rituximab is cost-effective (cost per LYG <€30 000) in patients with resistant or recurrent follicular lymphoma responding to induction treatment, in comparison to the usual practice of observing patients' evolution.

Key words: Cost analysis. Rituximab. Observation. Lymphoma, Follicular.

Análisis farmacoeconómico de rituximab en el tratamiento de mantenimiento de los pacientes con linfoma folicular

Introducción: En pacientes con linfoma folicular refractario o en recaída que responden a terapia de inducción con CHOP o rituximab + CHOP, el tratamiento de mantenimiento con rituximab frente a la opción de "observar" mejora la supervivencia global y la supervivencia libre de progresión.
Objetivo: Estimar si el tratamiento de mantenimiento con rituximab es una intervención coste-efectiva en comparación con la práctica clínica de "observar" su evolución.
Método: Población: la del ensayo clínico EORTC 20981. Perspectiva: Sistema Nacional de Salud Español (costes directos sanitarios). Diseño: Análisis coste-efectividad incremental, con un modelo de transición entre estados de salud. Variables principales: coste de ganar un año de vida ajustado por su calidad (AVAC), por año de vida ganado (AVG) y por AVG libre de progresión. Premisas del caso básico: distribución de Weibull para extrapolación de supervivencia, 5 años de duración del beneficio del tratamiento, horizonte temporal de 10 años y tasa anual de descuento (costes y beneficios) del 3,5%. Estas premisas se modificaron en los análisis de sensibilidad.
Resultados: Análisis determinístico: el coste por AVAC ganado fue de 9.358 €, por AVG de 8.493 € y por AVG libre de progresión de 5.485 €. Análisis probabilístico y de sensibilidad: confirmaron la estabilidad de los resultados del análisis determinístico.
Conclusiones: Según este modelo, el tratamiento de mantenimiento con rituximab es coste-efectivo (coste por AVG < 30.000 €) en los pacientes con linfoma folicular resistente o en recaída que responden al tratamiento de inducción, en comparación con la práctica habitual de observar la evolución de los pacientes.

Palabras clave: Análisis de costes. Rituximab. Observación. Linfoma folicular

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INTRODUCTION

Non-hodgkin's lymphoma (NHL) is an extremely heterogeneous group of neoplasias of the lymphoid system. In accordance with the World Health Organisation classification, follicular lymphomas (FL) are found among the B-cell NHL and they are characterised by their indolent course, long survival times (8-12 years), although they are refractory to chemotherapy for which the response rates are very low. The incidence of FL is quickly increasing in industrialised countries, with a mortality rate in Spain of 5.5 cases and 3.6 cases per 100 000 in men and women respectively.[1]

Treatment of FL varies greatly and includes options like radiotherapy and polychemotherapy. In addition to active treatment, the existence of spontaneous regression, its not-very-aggressive or indolent clinical course and the frequency of asymptomatic periods mean that conservative, watchful waiting attitudes are often taken in the cases of asymptomatic patients.[2,3]

During recent years, the introduction of a new therapeutic option, immunotherapy with monoclonal antibodies, has allowed the treatment to be made more specific, reducing toxicity and also presenting synergism with conventional chemotherapy thanks to its different mechanism of action.

Rituximab (Mabthera®), the first murine/human monoclonal antibody against the CD20 marker for NHL, is indicated in the treatment of patients with stage III-IV FL, who are resistant to chemotherapy or are in their second or third relapse following chemotherapy, in combination or not with the CHOP regime (cyclophosphamide + vincristine + doxorubicin + prednisone), as well as in combination with the CVP regimen (cyclophosphamide + vincristine + prednisone) in previously untreated patients.[4] It has recently been indicated as maintenance treatment in patients with recurring or refractory FL responding to induction treatment with chemotherapy, with or without rituximab.[4]

Approval was given for this indication mainly due to the results of a clinical trial performed by the EORTC intergroup (European Organization for Research and Treatment of Cancer), EORTC 20981.[5] This study was designed with 2 objectives: *a)* to research on the benefit of adding rituximab to the CHOP protocol (R-CHOP) for the treatment of advanced, chemotherapy resistant or relapsing FL (induction stage); and *b*) to find out if maintenance treatment with rituximab in monotherapy (375 mg/m in IV infusion, once every 3 months, to a maximum of 2 years or until relapse) in patients with a partial or complete response after previous induction, prolongs the duration of the response.[5] The study concluded that the progression-free survival median was greater with R-CHOP (33.1 months) than with CHOP (20.2 months) (P=.0003) in the induction stage, as it also was with rituximab (51.6 months) compared to observation (15.0 months) (P<.0001) in the maintenance stage. Furthermore, and most importantly, overall survival was greater in the maintenance group with rituximab, with 85.1% alive after 3 years in comparison to 77.1% in the observation group (P=.011) (Table 1).[5]

The cost of the diagnosis-related group (DRG) 401, which includes FL, is €7272, updated in 2006.[6] The importance of this figure and the socioeconomic repercussions of FL, justify the making of pharmacoeconomic analyses using models that help to determine the effectiveness of the different treatments available.[7]

The purpose of this work was to determine if maintenance treatment with rituximab is a cost-effective intervention in comparison with the "watchful waiting" or "observation" clinical practice, in patients with resistant or recurrent FL, having responded to induction treatment with CHOP or R-CHOP.

METHOD

Pharmacoeconomic Model

The study consisted of a pharmacoeconomic model, understood as a theoretical scheme that allows simulations of drug-related complex healthcare processes to be made, and which is prepared following a pre-established protocol, using estimations obtained from the available data (published or not) on effectiveness, toxicity, and costs of the alternatives compared.[7] An international transition model between states of health was adapted to the Spanish healthcare system, the structure of which is set out in Figure and which is described in greater detail below.

Target Population

It represents the hypothetical group of patients subjected to the theoretical analysis, and therefore, the population to which the results of the study can be applied. The target population consisted of patients of both genders, diagnosed with resistant or recurring FL (stages II or IV), who have responded to induction treatment with 6 cycles of the CHOP or R-CHOP schedules, according to the characteristics of the patients in the clinical trial EORTC 20981, the results of which were used in the pharmacoeconomic model (Table 1).[5]

States of Health

In the model, in accordance with the natural history of FL, the following states of health were considered (Figure): 2 "transition" states (progression-free [PF] and disease progression [DP]) in

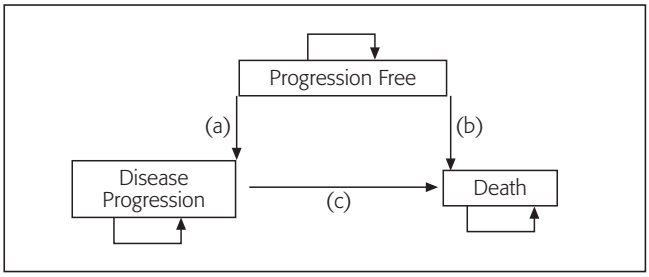

Figure. *Structure of the pharmacoeconomic model for transition between states of health. The (a), (b), and (c) transitions were obtained from those observed in the EORTC 20981 clinical trial.*

which the patients could remain for several 1-month cycles, and the so-called "absorbent" state (the death [D] of the patients) (Figure). All the patients in the cohort were initially progression free. Throughout the monthly cycles, the patients could continue in this state [PF] or transfer to the other 2 states (DP and D); once progression starts, the patient can stay in this state (DP) or die (D).

The objective of the model was to estimate the differences between the therapeutic options (maintenance with rituximab or "observation") compared within the following aspects: *a*) quality-adjusted life years (QALY); *b*) life years without quality adjustment (LY); *c*) the time during which the patients survive without progression of the disease (years of progression-free survival, YPFS); as well as *d*) the costs associated with PF and DP states. The costs associated with death (M) were not considered.

It must be highlighted that the model does not follow the usual Markov procedure, as it does not use the transition probabilities among the states,[8] but directly uses the PF and survival times, estimated using the Kaplan Meier method. Therefore, the model calculates the area under the time curve in which patients stay alive in the PF and DP states.

Effectiveness Data and Type of Analyses

The type of pharmacoeconomic or drug cost analysis which must be performed depends on whether or not any differences have been shown in effectiveness or toxicity among the treatments. As was indicated above, the EORTC 20981 study, the characteristics of which are set out in Table 1, concluded that in the maintenance stage: *a*) the progression-free survival median was higher with rituximab (51.6 months) in comparison with the observation group (15.0 months) ($P<.0001$); and *b*) there were also differences in survival at 3 years favouring rituximab (85.1% compared to 77.1%; $P=.011$).[5] The patients on maintenance treatment with rituximab also had more adverse events than those in the observation group (Table 1).

Because differences in survival have been shown among the therapeutic options compared, a cost-effectiveness analysis was performed (cost per life year gained, LYG, cost per YPFS gained). On the other hand, a cost-utility analysis was carried out due to the fact that the different rate of progression of the disease and the differences in toxicity compared between the patients in

Table 1. Characteristics of the Patients and Effectiveness and Toxicity Outcomes of the Stage III Randomised EORTC 20981 Clinical Trial. Second-Line Maintenance Treatment of Resistant or Recurrent Non-Hodgkin's Follicular Lymphoma, in Stages III and IV[a]

Item	Maintenance Stage	
	Observation	Rituxima[b]
Characteristics of the patients and prognostic factors		
Number of patients	167 CHOP/R-CHOP: 41%/59%	167 CHOP/R-CHOP: 46%/55%
Response to induction	CR/PR:29%/71%	CR/PR:29%/71%
FLIPI 2	–	–
≥3	–	–
≥2	70%	66%
Main effectiveness and toxicity outcomes		
Progression-free survival, months[b]	15.0	51.6[c]
Survival at 3 years[b]	77.1%	85.1%[c]
Neutropaenia		
Stage 3	6.0%	12.6%
Stage 4	3.6%	4.8%
Infection		
Stage 3	1.8%	7.2%
Stage 4	0.6%	1.8%

[a]CHOP indicates every 21 days, for 5 days, the following cycle is administered (6 cycles maximum): cyclophosphamide (750 mg/m^2 iv day 1), doxorubicin (50 mg/m^2 iv day 1), vincristine (1.4 mg/m^2 iv day 1), and prednisone (100 mg/d, days 1-5); FLIPI, Follicular Lymphoma International Prognostic Index; CR, complete response; R-CHOP, CHOP protocol, plus rituximab (375 mg/m^2 iv, on day 1 of each cycle); PR, partial response.
[b]From the second randomisation in the maintenance stage.
[c]$P<.0001$
[d]$P=.011$.

maintenance with rituximab and those being observed, could have repercussions on quality of life, and, therefore on utility values (QALY).

The comparison of incremental cost-effectiveness and cost-utility outcomes were made by applying the following formula:

$$\frac{\text{(Costs per patient in maintenance with rituximab – Cost per patient in observation)}}{\text{(AV, YPFS, or QALY per patient in maintenance with rituximab - AV, YPFS, or QALY per patient under observation)}}$$

The outcomes are presented as incremental costs, cost per QALY gained (cost-utility), and as cost per life year gained (LYG) or cost per YPFS gained (cost-effectiveness) with the maintenance treatment with rituximab, in comparison with the "watchful waiting" approach.

Estimation of Utility Values

Utility values were measured as quality-adjusted life years (QALY), a QALY being a year of life multiplied by a weighting factor indicating the quality of life of the person during that year. The "weight" or weighting factor of the quality of a life year can range from 0 (death or an equivalent state) to the value 1 (which indicates perfect health). The utility values used in the model (Table 2) were taken from a study performed in the United Kingdom, in 152 patients with FL, to whom the analogue visual scale of the EQ-5D instrument was administered.[9] The utility values of PF and DP states of health, estimated by the York rate, are indicated in Table 2.

Duration of the Cycles, Time Horizon, and Discounts

Transitions between states were performed in some discreet time periods called "cycles" which, as has been said above, had duration of 1 month in the model. In the basic case of the analysis, the maximum duration of the maintenance treatment with rituximab was 2 years (approximately the EORTC 20981 study follow-up median).[5]

The time horizon of the basic case of the analysis was 10 years. This was chosen as it was considered that it reflected the average survival of the target population studied. However, in the sensitivity analysis a lapse of 30 years was also considered to simulate the life-time evolution of the theoretical cohort of patients.

In order to estimate the duration of the treatment benefit (5 years in the basic case) and to develop a 10-year follow-up model in the basic case and for life in the sensitivity analysis, it was necessary to extrapolate the Kaplan Meier data obtained in the clinical trial, through parametric extrapolations using the Weibull (basic case) and Log-logistic (sensitivity analysis) distributions.[10]

An annual discount of 3.5% was made for the costs and benefits (QALY, LY and YPFS) according to the recommendations of the National Institute for Clinical Excellence (NICE).[11] Both were counted in the middle of each cycle.

Table 2. Utilities Used in the Model in Advanced Follicular Lymphoma[a]

States of Health	Utility	N[b]
Progression-free survival	0.805	132
Disease progression	0.618	33
Death	0.000	–

[a]Source: Study of Oxford Outcomes, which calculated the utility values of the EQ-5D instrument, using the York rate.[9]
[b]N indicates sample size.

Study Perspective and Directives Followed

The study was performed from the perspective of the Spanish National Health System (NHS), therefore considering only direct healthcare costs.

The general directives for performing pharmacoeconomic analyses in Spain were followed,[7] as well as the directives published by the Canadian Agency for Drugs and Technologies in Health (CADTH)[12] and the Principles of Good Practice for modelling of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).[13]

Cost Estimate

The cost estimate of a disease treated with a certain drug is done by identifying and quantifying healthcare resources involved and assigning the resources to specific unit costs. This is how the average costs for a patient with advanced FL were estimated. The cost of healthcare resources used in the model are presented in euros (€) dated May 2006.

Only annual costs were considered based on a randomisation of the patients to the maintenance with rituximab group or the observation group in the EORTC 20981 clinical trial. The use of resources and their unit costs are set out in Table 3.

Four types of costs were analysed: *a*) purchasing and administering rituximab (estimated using rates of use: number of doses received per patient); *b*) adverse events (AE) (obtained from their frequency with rituximab or observation, by unit costs of their groups related to the diagnosis or DRG: serious AE were calculated individually and the unit cost of the other AE was estimated as the cost of an outpatient haematology consult); *c*) post-progression treatments (rescue treatments administered after progression of the disease following maintenance treatment with rituximab or observation and until death); and *d*) costs of routine management and monitoring of the patients (Tables 3 and 4).

The use of healthcare resources and post-progression treatments were estimated (for the basic case of the analysis) by a panel of 8 Spanish oncohaematologists (Table 4). They were asked the following questions: *a*) place where the maintenance treatment with rituximab was administered; *b*) average duration of

Table 3. Use and Unit Costs of Healthcare Resources (€ in May 2006) Used in the Pharmacoeconomic Model[a]

Item	Use of Resources Unit Costs, €	Reference
Maintenance treatment with rituximab		
Use of rituximab for maintenance		
Number of doses received per patient	Number of patients	
0	1	5
1	14	5
2	10	5
3	12	5
4	5	5
5	7	5
6	4	5
7	3	5
8	78	5
Total doses	794	Calculated
Number of patients	134	Calculated
Mean number of doses per patient	5.9254	Calculated
% of doses for the first year	58	5
% of doses for the second year	42	5
Cost of rituximab for maintenance		
Rituximab protocol for maintenance	375 mg/m2 in IV infusion, once every 3 months, to a maximum of 2 years	5
Average estimated body surface, mean (standard deviation)	1.70 m^2 (0.01)	15.16
Average dose of rituximab per patient and cycle	700 mg	Calculated
Minimum sale price (MSP) of 100 mg of rituximab	€250.81	14
Cost of 1 mg of rituximab	€2.51	Calculated
Cost per average dose of rituximab	€1755.67	Calculated
Total cost of rituximab per patient	€10 254.11	Calculated
Unit cost of day hospital for haematology (16 hours)	€321.66	6
Duration of the IV administration of rituximab	3 hours	4
Cost per IV administration of rituximab in day hospital per patient and cycle	€60.30	Calculated
Cost of a non-serious adverse event (1 haematology consultation)	€30.03	6
Total cost of administration of rituximab per patient	€352.19	Calculated
Adverse events in the maintenance stage		
Number of patients in the EORTC 20981 study	Rituximab: 167 Observation: 167	5
Number of serious adverse events observed in the EORTC 20981 study	Rituximab: 30 Observation: 1	5
Adverse events (number) and their unit costs, mean (minimum-maximum)		
Blood dyscrasias[1] (DRG 399)	€2388.42 (1664.25-2987.62)	6
Mild infections[2] (outpatient group: acute pharyngitis)	€30.03 (e30.03-30.03)	6
Bronchopneumonia without complications[6] (DRG 90)	€1978.41 (1189.48-3162.29)	6
Septicaemia[1] (DRG 416)	€5768.96 (2770.50-9913.02)	6
Other gastrointestinal disorders[3] (DRG 189)	€1864.97 (1189.48-2129.00)	6
Renal and urinary tract infections without complications[2] (DRG 321)	€1996.66 (1252.94-3669.46)	6
Central nervous system disorders without complications[2] (DRG 35)	€1986.11(690.74-3791.96)	6
Adverse events not assigned to DRG[1]	€2622.42 (1563.25-4220.22)	6
Pulmonary embolism, without complications[1] (DRG 78)	€4193.15 (3751.88-4804.21)	6

(Continued)

Table 3. Use and Unit Costs of Healthcare Resources (€ in May 2006) Used in the Pharmacoeconomic Model[a] (*Continued*)

Item	Use of Resources Unit Costs, €	Reference
Skin disorders without complications[1] (DRG 284)	€1907.72 (1059.47-3509.11)	6
Osteomuscular pain[1] (PMC 4708)	€2223.01 (2223.01-2223.01)	6
Heart failure without complicationsb,[1,2] (DRG 127)	€3259.24 (1822.61-5846.73)	6
Ischaemic heart disease without intervention[1] (DRG 140)	€2474.22 (858.65-5487.53)	6
Upper respiratory tract infections without complications[1] (DRG 69)	€1286.09 (580.03-1953.06)	6
Acute hepatic disorder[1] (DRG 205)	€3066.95 (1273.58-4912.74)	6
Acute myocardial infarct without complications[2] (DRG 122)	€5574.76 (3335.23-11 397.03)	6
Asthma without complications[1] (DRG 97)	€1833.42 (1042.20-2705.63)	6
Malignant breast neoplasia without complications[1] (DRG 275)	€2748.11 (1841.16-3221.32)	6
Use of healthcare resources (see Table 4)		
Post-progression treatments (see Table 4)		

[a]EORTC, European Organization for Research and Treatment of Cancer; DRG, diagnosis related group; PMC, patient management categories; MSP, minimum sale price.
[b]Two cases in the rituximab group, 1 case in the observation group.

intravenous perfusion with rituximab; *c*) frequency of medical consultations according to the patient's state of health; *d*) rescue treatments in patients relapsing after the period of maintenance with rituximab or observation (post-progression treatments); and *e*) frequency of administration of these treatments.

In order to calculate the purchase cost of rituximab, minimum sale prices (MSP)[14] and the dosing regimens of the EORTC 20981 study[5] were used for an average body surface area of 1.7m^2, a value that was estimated in accordance with the statistical data from the Ministry of Health and Consumer Affairs on height and weight of the Spanish population[15] as the mean of the results obtained with several ad hoc formulae[16] (Table 3). The cost of post-progression treatments was estimated according to the dose and mean number of cycles recommended in the drug technical specifications.

The other unit costs (medical consultations, day hospital, DRG) were obtained based on a Spanish healthcare costs database.[6]

Sensitivity Analysis

In order to check the stability of the results and the consistency of the estimations made, sensitivity analyses were made for the following variables: *a*) the type of analysis (probabilistic instead of a simple single-factor analysis)[17]; *b*) the type of distribution (Log-logistic instead of Weibull); *c*) the number of the model years in which survival was calculated by the Kaplan Meier method (the calculation of survival in the following years was obtained by parametric curves); *d*) the duration of the therapeutic benefit (2, 3, 10, 20, and 30 years, instead of 5 years); *e*) the time horizon of the simulation (4, 7, 15, 20, and 30 years, instead of 10); *f*) minimum and maximum costs for healthcare resources and adverse events (instead of average costs); *g*) variations in the utility values of PF and DP states; *h*) not applying an annual discount rate to the costs and benefits (instead of 3.5% for both); *i*) consider the post-progression treatments used in the EORTC 20981 clinical trial instead of the estimations from the panel of experts; and, finally, *j*) varying the interval between post-progression treatments between 1 and 5 years (instead of 2 years).

A probabilistic sensitivity analysis was made and the 95% confidence intercal (CI) was calculated for the cost-utility ratio, by 2000 iterations via simulation which enabled us to guarantee the stabilisation of standard deviations.

Finally, the acceptability curve of the incremental cost-effectiveness was analysed[17] considering that a new treatment would be reimbursed by the National Health Service System for an incremental cost-effectiveness threshold equal to or below €30 000 per QALY gained or per LYG, in accordance with a Spanish study that analysed 100 economic assessments performed in Spain between 1999 and 2001.[18]

RESULTS

Cost Analysis

In the basic case, the mean cost per patient in maintenance with rituximab was €22 458.20 and €14 432.14 in the observation group, with an incremental cost with rituximab of €8026.60 (Table 5). In addition to the purchase cost of the treatment, in the rituximab group there were also higher costs caused by adverse events. On the contrary, the costs were higher in the observation groups regarding the post-progression treatments stage (€3032.44 more) (Table 5).

Effectiveness Analysis

In the basic case, more QALY, more LY, and more YPFS were obtained per patient in maintenance with rituximab than with

Table 4. Results of the Estimations of the Panel of Spanish Experts on the Use of Healthcare Resources and Post-Progression Treatments in the Spanish Healthcare Setting[a]

Use of Healthcare Resources		Values Mean	Minimum-Maximum Values
Place where the rituximab maintenance treatment is administered		Day hospital: 99.4% Haematology Department: 0.6%	–
Average duration of intravenous perfusion of rituximab, minutes		183	138-270
No. of monthly medical consultations per progression-free patient (maintenance group)		0.33	0.33-0.33
No. of monthly medical consultations per progression-free patient (observation group)		0.29	0.17-0.33
No. of medical consultations per relapsing patient		1.06	0.67-2.00
Average interval between the third and fourth line of treatment, years		2	1-4
Post-Progression Treatments	**Item**	**Maintenance With rituximab**	**Observation**
The most commonly-used rescue treatments, in patients previously responding to induction therapy, relapsing after... ,%	Chemotherapy	40.57	18.86
	Monotherapy with rituximab	3.71	13.43
	Rituximab + chemotherapy	31.14	47.71
	Allogeneic HSCT	2.86	1.14
	Autologous HSCT	10.00	4.71
	HSCT+rituximab	1.79	2.64
	Chemoradiotherapy	3.00	6.43
	Chemotherapy+interferon	1.36	0.93
	Radiotherapy	5.57	4.14
The most commonly-used chemotherapy regimens, in patients previously responding to induction therapy, relapsing after...,%	ESHAP	39.00	40.00
	FC	–	14.00
	FM	22.00	8.00
	CVP	8.00	6.00
	MVP	6.00	5.00
	HyperCVAD	6.00	6.00
	Chlorambucil	4.00	2.00
	FMD	4.00	–
	CHOP	3.00	–
	GEMOX	2.00	–
	FMC	2.00	2.00
	Fludarabine	2.00	6.00
	Oral cyclophosphamide	2.00	2.00
	Gemcitabine	–	2.00
	Others	–	5.00
The most commonly-used chemotherapy regimens (in combination with rituximab), in patients previously responding to induction therapy, relapsing after...,%	R-FM	35.00	17.50
	R-FC	15.00	20.00
	R-MVP	15.00	7.50
	R-HyperCVAD	15.00	7.50
	R-ESHAP	10.00	23.75
	R-CHOP	5.00	16.25
	R-FCM	5.00	2.50
	R-FMD	5.00	2.50

[a]CHOP indicates cyclophosphamide-doxorubicin-vincristine-prednisone; CVP, cyclophosphamide-vincristine-prednisone; ESHAP, etoposide-methylprednisolone-cisplatin; FC, fludarabine-cyclophosphamide; FM, fludarabine-mitoxantrone; FMC, FM plus cyclophosphamide; FMD, FM plus dexamethasone; GEMOX, gemcitabine-oxaliplatin; HyperCVAD, cyclophosphamide-mesna-doxorubicin-vincristine-dexamethasone-GCSF (cycle 1) and methotrexate-cytarabine-folic acid (cycle 2); MVP, mitoxantrone-etoposide-prednisone; R, rituximab; HSCT, haematopoietic stem cells transplantation.

Table 5. Outcomes of the Deterministic Analysis Basic Case on Second-Line Maintenance Treatment With Rituximab, Compared to Observation, in Patients With Non-Hodgkin's Follicular Lymphoma (€ May 2006)[a]

Variables	Rituximab	Observation	Difference
Costs distribution, €			
Treatments, including administration	10 612.17	0.00	10 612.17
Adverse events	498.05	62.85	435.19
Post-progression treatments	8292.88	11 325.31	-3032.44
Routine management, patient monitoring	3055.11	3043.97	11.14
Cost per patient, €	*22 458.20*	*14 432.14*	*8026.06*
Quality-adjusted life years (QALY)	4.1133	3.2557	0.8576
Cost per QALY gained, €	*9358.49*	–	–
Life years (LY)	5.6891	4.7441	0.9450
Cost per life year gained (LYG), €	*8493.18*	–	–
Years of progression-free survival (YPFS)	3.1952	1.7320	1.4632
Cost per year of YPFS, €	*5485.39*	–	–

[a]QALY indicates quality-adjusted life year; LYG, life-year gained; YPFS, year of progression-free survival.

simple observation (0.8576; 0.9450; and 1.4632, respectively) (Table 5).

Incremental Cost-Utility and Cost-Effectiveness

In the basic case, the cost per QALY gained with the more effective treatment (maintenance with rituximab) was €9358, the cost per LYG was €8493, and the cost per YPFS gained was €5485 (Table 5).

Sensitivity Analysis

The outcomes of the sensitivity analysis were, in all cases, below €30 000 per QALY gained, with values ranging from €5823 (1 year interval between post-progression treatments) or €7 263 (extension of the treatment benefit to 30 years), and €22 160 (reducing treatment benefit to the 2-year duration of the clinical trial) per QALY gained (Table 6).

The probabilistic sensitivity analysis confirmed the result of cost-utility of the basic case. In this analysis, the following outcomes were obtained (mean [standard deviation]; minimum-maximum): costs per patient in maintenance with rituximab of €22 181.72 (€1885.58) (€15 296.55-€28 981.40) and in observation, €14 280.98 (€1781.79) (€8282.25-€21 912.79); and values of QALY with rituximab of 4.0694 (0.3818); (2.5045-5.1340) and with observation of 3.2336 (0.3159); (2.2208-4.2690). The mean cost per QALY gained was ε9323 (95% CI, €9282-€9364). Rituximab was more effective, with higher costs for the observation group, in 100% of the simulations made, as can be seen in the acceptability curve of the incremental cost-effectiveness, which was below the €30 000 threshold per QALY gained.[18]

DISCUSSION

According to the results of this model, maintenance treatment with rituximab is cost-effective in patients with resistant or recurrent follicular lymphoma responding to induction treatment, in comparison to the usual practice of observing patients' evolution.

When assessing these results, we must firstly consider that this is a theoretical model (which is, by definition, a simplified simulation of the actual situation) based, however, on the outcomes of a randomised clinical trial that directly compared the options studied, with a non-pragmatic design. For this reason, it is especially important that the model be validated by a panel of Spanish oncohaematological experts who estimated the use of resources in clinical practice in this country, so the results must be considered as valid estimations for patients with the characteristics of those included in the EORTC 20981 clinical trial, which could be useful as a tool for making decisions in clinical practice.[7]

One aspect that must be mentioned is the fact that the utilities of the states of health used in the model were obtained from a study in the United Kingdom. Although preferences for states of health can vary among countries, due to cultural factors[12] this risk is lower when countries with similar social and economic levels are compared.

On the other hand, it must be taken into account that, thanks to the transition model, it was possible to estimate the evolution of the disease over 2-30 years[19] in a more "realistic" manner than with a purely deterministic model. In the same way, we would indicate as "strengths" of this model the fact that the estimation of unit costs for healthcare resources and adverse events was made using a Spanish databases[6,14] using DRG and that utilities were obtained by an appropriate method, from patients with follicular lymphoma.

In order to try to minimise the model limitations, conservative premises were taken in the basic case and simple single-factor sensitivity and probabilistic analyses were made, that confirm the stability of the premises considered in the basic case. In this case, the costs of post-progression treatments were higher in the observation group (€3032 more). This difference was confirmed both in the estimations of the post-progression treatments (rescue treatments) of the panel of experts and when the treatments administered in the EORTC 20981 study were used in the model (with additional costs in the observation group of €2910). In this respect, it is worth mentioning the great variability observed in the post-progression treatments used by the expert consulted, which reflects the true situation in usual clinical practice. This variability did not affect the stability of the outcomes obtained in the basic case of the analysis.

In addition to the EORTC 20981 study, the results of 3 other clinical studies are currently available, which were used to assess

Table 6. Sensitivity Analysis of the Pharmacoeconomic Model for Second-Line Maintenance Treatment of Advanced Follicular Lymphoma With Rituximab (Cost per QALY Gained; € May 2006)[a]

Settings	Cost per QALY Gained, €
Basic case	9358
Probabilistic analysis (basic case: simple single-factor)[b]	9323
95% CI	9282-9364
Extrapolation of the survival values with a Log-logistic distribution (basic case: Weibull)	8685
Number of years of the model in which survival is calculated with Kaplan Meier (basic case: 2 years)	
1 year	9999
4 years	9541
Duration of the treatment benefit (basic case: 5 years)	
2 Years	22 160
3 Years	14 680
10 Years	7263
20 Years	7263
30 Years	7263
Time horizon of modelling (basic case: 10 years)	
4 Years	21 681
7 Years	10 210
15 Years	9199
20 Years	9192
30 Years	9192
Unit costs of healthcare resources and adverse events (basic case: means)	
Minimums	9148
Maximums	9715
Use of the progression-free survival state (basic case: 0.805): 0.618	13 743
Use of the disease progression state (basic case: 0.618): 0.805	10 550
Without annual discount of costs and benefits (basic case: 3.5%): 0.0%	8193
Post-progression treatments (basic case: estimations by the panel of experts): Those administered in the EORTC 20981 clinical trial	9442
No. of years between post-progression treatment (rescue treatment after relapse following maintenance 2) treatment or observation) (basic case):	
1 Year	5823
5 Years	11 480

[a]QALY indicates quality-adjusted life years; 95% CI, 95% confidence interval.
[b]Rituximab was the most effective, with higher costs in the observation group, in 100% of the simulations.

the effectiveness of maintenance treatment with rituximab in patients with follicular lymphoma: the LYM-5[20] SAKK,[21] and GLSG-FCM[22] studies. The only data used in the model were those from the EORTC 20981 study[5] because they provide higher quality clinical evidence due to the larger size of the sample, which allowed us to find statistically significant differences.

Only 1 pharmacoeconomic study has been identified in the second-line maintenance treatment of follicular lymphoma,[23] prepared using the same model as in this study, obtaining a cost per QALY gained of 20 428 Canadian dollars (around €13 000). The difference from the results of the Spanish model (€9358 per QALY gained) may be attributed both to variations between the healthcare systems and the different costs of the resources in both countries.

It is important to put in context the cost of around €9000 per QALY gained, obtained for maintenance treatment with rituximab of a patient with follicular lymphoma. For this, comparing these costs per QALY gained with that of drugs from other therapeutic

groups may be illustrative. In this respect, it must firstly be mentioned that according to 2 Spanish studies in 1995 and 1998, in this country the examples used were 2 hypolipidemic agents financed by the NHS, with a maximum cost per year of life gained varying between €66 000 and €240 000.[24,25] Also, according to a review of the year 2002[18] other healthcare interventions were also above the cost per QALY for maintenance with rituximab, such as pneumococcal vaccination in the group aged from 5 to 44 years of age (€69 416),[26] treatment with alteplase against streptokinase in myocardial infarct (€10 870-€72 471)[27] or the hormone replacement therapy against non-treatment in women aged 50 years (€19 562)[28] in euros updated for the year 2006.

The outcomes of this pharmacoeconomic analysis must be confirmed in pragmatic, randomised clinical trials, where a direct comparison is made of effectiveness, utilities, tolerance, and consumption of healthcare resources of the alternative therapies assessed. In the meantime, in accordance with the results of the model, it can be concluded that, in comparison with the "watchful waiting" option, maintenance treatment with rituximab (in addition to improving progression-free survival) would provide more quality-adjusted life years (QALY) at an average cost per QALY of €9358, in patients with resistant or recurring advanced follicular lymphoma that have previously responded to CHOP or R-CHOP.

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