Cost-effectiveness Analysis of Rituximab Maintenance Treatment in Patients With Follicular Lymphoma who Respond to First Line Induction Therapy in Portugal

Análise de Custo-efetividade de Rituximab no Tratamento de Manutenção de Doentes com Linfoma Folicular, Com Resposta à Terapêutica de Indução em Primeira Linha, em Portugal

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Recebido: 6/8/2015; Aceite: 23/12/2015.

Abstract

Introduction: To perform a cost-effectiveness analysis of follicular lymphoma maintenance treatment after first-line induction with rituximab compared to observation in Portugal.

Methods: A Markov follicular lymphoma model was developed with four health states: progression free survival on first and second lines, progression and death. The transition probabilities between health states were obtained from the PRIMA and EORTC20981 clinical trials and the health states utilities from the literature. The analysis considered the Portuguese National Health Service perspective and includes only direct costs. Resource consumption was estimated by a Portuguese clinical expert panel. The unit costs (€ in 2014) were estimated using Portuguese official databases. Deterministic and probabilistic analyses were performed.

Results: In the base case, for a time horizon of 10 years, the cost per life year gained and per quality-adjusted life-year were € 10,634 and € 10,664, respectively. The sensitivity analyses confirmed the stability of the base case for time horizons of 20 and 30 years, varying between € 7,430 and € 7,155. Maintenance with rituximab is cost-effective for a time horizon of 5.5 years (cost per quality-adjusted life-year gained of € 23,616).

Conclusion: According to the present model rituximab maintenance treatment of follicular lymphoma patients that respond to first line induction therapy in comparison with observation is cost-effective in Portugal.

Keywords: Cost-Benefit Analysis; Follicular Lymphoma; Portugal; Rituximab.

Resumo

Introdução: Realizar uma análise de custo-efetividade de rituximab no tratamento de manutenção do linfoma folicular após indução em primeira linha, em comparação com observação, em Portugal.

Métodos: Desenvolveu-se um modelo de Markov para o linfoma folicular com quatro estados de saúde: sobrevivência livre de progressão, após primeira e segundas linhas, progressão e morte. As probabilidades de transição entre estados de saúde foram obtidas a partir dos ensaios clínicos PRIMA e EORTC20981 e

as respetivas utilidades a partir da literatura. A perspetiva da análise foi a do Serviço Nacional de Saúde português e incluiu apenas os custos diretos. O consumo de recursos foi estimado por um painel de peritos constituído por clínicos portugueses. Os custos unitários (€ em 2014) foram estimados usando bases de dados oficiais portuguesas. Realizaram-se análises determinísticas e probabilísticas.
Resultados: No cenário base, para um horizonte temporal de dez anos, os custos por ano de vida ganho e por ano de vida ajustado pela qualidade foram de € 10 634 e € 10 664, respetivamente. As análises de sensibilidade confirmaram os resultados do cenário-base para horizontes temporais de 20 e 30 anos, variando entre € 7430 e € 7155. O tratamento de manutenção com rituximab é custo-efetivo para um horizonte temporal de 5,5 anos (custo por ano de vida ajustado pela qualidade ganho de € 23 616).
Conclusão: De acordo com o atual modelo, o tratamento de manutenção com rituximab em doentes com linfoma folicular que responderam à terapêutica de indução em primeira linha, em comparação com a observação, é custo-efetivo em Portugal.
Palavras-chave: Análise Custo-Benefício; Linfoma Folicular; Portugal; Rituximab.

Introduction

Non-Hodgkin's follicular lymphoma (FL) is a cancer associated with the B-cells of the germinal center of the lymph node. It is the second most common lymphoma sub-type that is known for its indolent course, with long median survivals up to 14 years.[1,2]

Despite the high response rate to the initial treatment, the majority of patients relapse afterwards. Approximately 80% of patients are diagnosed with advanced disease (stages III or IV)[3] and considered incurable with conventional treatments. For these patients the objective is to accomplish "optimal palliative care" with the aim of prolonging survival and achieve long periods free of disease symptoms, reduce both the chemotherapy toxicity and the psychological burden of active life-threatening illness.[4]

Taking into account that a) some people may not require treatment for 20 years or more and b) the natural course of the disease with spontaneous remissions between 15 and 20% of cases in some asymptomatic patients a conservative (or "watch and wait") approach is taken.[1-4]

In symptomatic patients and in an attempt to alter the course of the disease, a different treatment approach in lymphoma therapy consists on a maintenance treatment after patients achieve an adequate response in induction. This maintenance treatment must be seen as part of an integrated approach in the management of these patients.

Over the last few years the introduction of a new treatment option – immunotherapy with monoclonal antibodies – has led to an increase in treatment specificity, reduced toxicity and also synergistic effects with conventional chemotherapy due to their distinct mechanism of action.[5] Thus, it has currently been demonstrated that the best therapy for FL patients with treatment criteria is the association of rituximab (first rodent/human chimeric monoclonal antibody directed against antigen CD20 for non-Hodgkin's lymphoma) with chemotherapy.[6] More recently, the results of the PRIMA (Primary RItuximab and MAintenance) clinical trial indicates that maintenance treatment with rituximab in FL patients that respond to first line induction regimens (R-CHOP, R-CVP or R-FCM) increases the progression free survival with a hazard ratio of 0.55 (95% CI; 0.44-0.68; p <0.0001) in comparison with observation.[7] Thus, maintenance with rituximab has become a formal therapeutic indication. However, pharmacoeconomic studies that exactly assess the economic impact and the real clinical benefit of this new therapeutic approach are still limited.

In this context, the purpose of this study is to perform a cost-effectiveness analysis of rituximab maintenance first line treatment in patients with FL receiving rituximab plus chemotherapy compared to observation in Portugal.

Methods

Pharmacoeconomic Model

The study consisted of a pharmacoeconomic model that allows simulations to be made of complex healthcare processes associated with medicinal products. This model was prepared, following a previously established protocol, using estimations obtained from the available data on the efficacy, toxicity and costs associated with the alternatives being compared.[8] An adaptation of an international Markov model was developed for the Portuguese

Health System[9,10] with a structure that is shown in Fig. 1 and described later in more detail. The transition probabilities between the model health states were obtained from the PRIMA and EORTC20981 clinical trials,[7,11] costs and resources use consumption from Portuguese sources and the health states utilities from the literature.

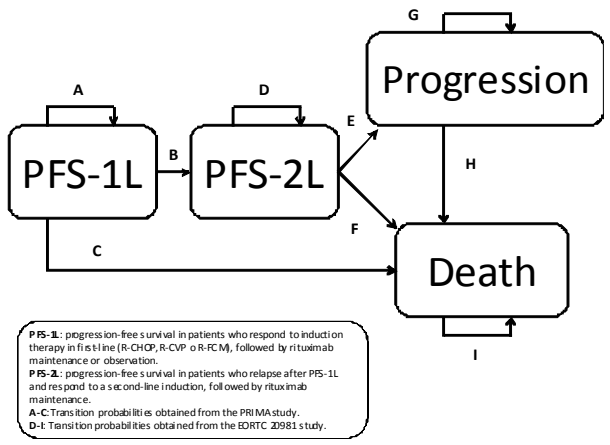

Figure 1 – Structure of the Markov model for the simulation of rituximab maintenance treatment of follicular lymphoma patients that respond to first line induction therapy (see also Table 2)

Target Population

It represents a hypothetical group of patients on whom the theoretical analysis is performed and, therefore, the population to which the results of the study may be applied. The target population was patients assumed to have the same baseline characteristics as those observed in the PRIMA clinical trial (summarized in Table 1): diagnosis of FL (grades I, II or IIIa) and who had a response (complete or partial) to first line induction with R-CHOP, R-CVP or R-FCM regimens. The PRIMA clinical trial results were used in the pharmacoeconomic model (Table 1).[7]

Health States

In accordance with the natural history of the FL disease, the model considered the following health states (Fig. 1): three "transient" states (progression free survival on first line [PFS-1L] or second line [PFS-2L] treatment and disease progression [progression]), in which the patients could remain on several cycles of 1 month duration, and the so-called "absorbing" state – death. Based on the randomized phase of the PRIMA clinical trial patients entered the model following an adequate response (complete or partial)

Table 1 – Principal premises and assumptions made in the pharmacoeconomic analysis performed using a Markov model

Item	Reference
1. Health states of the model: PFS-1L, PFS-2L, progression, death (Fig. 1)	9
2. Patients with follicular lymphoma who respond to first line induction therapy with R+CT regimen	7
3. Mean age (56.0 years) body weight (71.15 kg) and height (162.75 cm) of the cohort	7,25,26
4. Maintenance regimen with rituximab: 375 mg/m2 every 8 weeks during 2 years compared to observation	7
5. Transition probabilities considered in the model: see Table 2	7,11
6. Transition cycle duration: monthly, with mean cycle correction	9
7. Time horizon analysis: until death or 30 years (it is estimated that only 5% of the cohort would survive to that period)[10-30 years]*	14
8. Weibull model for the extrapolation of the permanency in PFS or the transition to progression or death, in the time horizon (calculated from the transition probabilities) [gamma, exponential, log-logistic, log-normal and Gompertz distributions]*	15
9. Mortality by all causes in Portugal (year 2014)	17
10. Ordinary least squares model to estimate the mortality from the progression state on second line	16
11. Health state utilities: PFS-1L: 0.880; PFS-2L: 0.790; progression: 0.620	12,13
12. Perspective of the analysis: Portuguese National Health Service	22
13. Rituximab price: 100 mg=€ 228.81; 500 mg=€ 1,138.93	24
14. Cost per patient of induction with the chemotherapy schemes (excluding rituximab): - CHOP=€ 372.02 - CVP=€ 146.19 - FCM=€ 773.32 - ESHAP=€ 254.42 - ICE=€ 515.73 - MINE=€ 127.19	24
15. Adverse events cost: according to the frequency observed in the PRIMA clinical trial and the unit costs of the corresponding DRGs for the moderate or severe adverse effects or the unit cost of a consultation in Primary Care in the case of mild adverse effects	22
16. Supportive care monthly costs - PFS P-1L, rituximab group: € 106 - PFS-1L, observation group: € 78.82 - PFS-2L: € 96.34	Expert panel
17. Annual discount rates for costs and utilities: 5% [0-6.0%]*	18

1L: first line treatment: 2L: second line treatment; PFS: progression-free survival; R-CT: rituximab + chemotherapy; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; CVP: cyclophosphamide, vincristine, prednisolone; FCM: fludarabine, cyclophosphamide, mitoxantrone; ESHAP: etoposide, methylprednisolone, high-dose cytarabine, cisplatin; ICE: ifosfamide-carboplatin-etoposide; MINE: mitoxantrone, mesna/ifosfamide and etoposide, DRG: diagnosis related groups: HR: hazard ratio.
* The values applied in the sensitivity analysis are shown between square brackets.

to induction therapy and start in the PFS-1L health state. Throughout the monthly cycles, patients may continue in that health state (PFS-1L) or transit to the other three states (PFS-2L, progression and death); once in the progression health state patients may remain in that state or die.
The purpose of the model was to estimate the differences between maintenance with rituximab and "observation" considering the following aspects: (i) the quality adjusted life-years (QALYs), (ii) the life years without adjusting for their quality (LY), (iii) the time during which the patients survived without disease progression as well as (iv) the costs associated with the health states PFS-1L, PFS-2L and progression. The costs due to death were not taken into consideration.

Efficacy Data and Types of Analysis

The type of pharmacoeconomic analysis that has to be performed depends on whether or not there are demonstrated differences in efficacy and toxicity between the treatments being compared. As mentioned previously the PRIMA clinical trial concluded that rituximab maintenance treatment in FL patients that respond to first line induction therapy with R-CHOP, R-CVP or R-FCM regimens increases the progression free survival compared to observation (Table 2).[7]
Thus, as clinical differences have been demonstrated between the compared treatment options, a cost-effectiveness analysis was performed (cost per life year gained, LYG). On the other hand, due to the different disease progression rate found between patients on rituximab maintenance and those under observation, this could have an impact on the quality of life and, therefore, in the utilities expressed as the QALYs, the cost-effectiveness is also evaluated as cost per QALY gained.
The comparison of the incremental cost-effectiveness results is made by applying the following formula:

$$\frac{\text{(Costs per patient on rituximab maintenance - Costs per patient under observation)}}{\text{(LY or QALY per patient on rituximab maintenance - LY or QALY per patient under observation)}}$$

The results are presented as incremental costs, LY gained, QALY gained, cost per LY gained and as cost per QALY gained with the rituximab maintenance compared with "wait and see" or observation.

Estimation of the Utilities

The utilities are measured as QALY; a QALY being one life year multiplied by a weighting factor that indicates the quality of life of the individual during that year. The "weight" or weighting factor of the quality of a life year may go from a value of 0 (death or an equivalent state) up to a value of 1 (which indicates perfect health). The utilities used in the model (Table 1) were taken from a study conducted in the United Kingdom on 152 patients with FL, to whom the visual analog scale of the EQ-5D tool was administered.[12,13]
The values of the utilities of the PFS-1L, PFS-2L and progression health states were estimated using the York tariff (Table 1).
In the model it is assumed that the loss of utilities due to adverse reactions would be negligible compared to the loss of utilities as a result of disease progression. For this reason, they were not considered in the calculations.

Table 2 – Transition probabilities in the model[7,11]

Transition (Fig. 1)	From	To	Previous treatment	Rituximab	Observation
A	Progression-free survival-first line*	Progression-free survival-first line*	-	1-(B+C)	1-(B+C)
B	Progression-free survival-first line	Progression-free survival-second line	RIT OBS	0.26 0.49	0.74 0.51
C	Progression-free survival-first line	Death	-	0.0003	0.0002
D	Progression-free survival-second line	Progression-free survival-second line	-	0.00118	0.00118
E	Progression-free survival-second line	Progression	RIT OBS	0.01927 0.01664	0.01850 0.05509
F	Progression-free survival-second line	Death	-	1-(D+E)	1-(D+E)
G	Progression	Progression	-	1-H	1-H
H	Progression	Death	-	0.02305	0.05016

*HR=0.55 (95% CI; 0.44-0.68). Legend: RIT: rituximab; OBS: observation.

Duration of Cycles, Time Horizon and Discounts

The transitions between health states in the model were made in discrete time periods called "cycles" that, as mentioned previously, had a 1 month duration.[9] In the base case the maximum duration

of the rituximab maintenance treatment was 2 years (according to the PRIMA clinical trial). [7]

The time horizon of the base case of the analysis was 10 years.[14] However, time periods of 20 and 30 years were also considered in the sensitivity analysis, that is to say, until the death of almost all the cohort and therefore capturing the full lifetime of an average FL patient. A threshold sensitivity analysis to estimate the minimum time horizon from which rituximab maintenance would be cost-effective was also performed.

In order to develop a model with a 10-year follow up in the base case, it was necessary to extrapolate the Kaplan-Meier data obtained from the clinical trial by using different statistical distributions: Weibull in the base case; exponential, log-logistic, log-Normal, Gompertz and gamma in the sensitivity analysis.[15] Parametric distributions were assessed for their goodness of fit to the data using the Akaike Information Criterion and graphical assessment of each parametric function.[15]

Due to the broad censoring of the overall survival in the PRIMA clinical trial (95% and 97% in the rituximab and observation groups, respectively) the progression or death probabilities in the second or third lines were obtained from the EORTC 20981 clinical trial.[11] In order to estimate the mortality from the progression state, an ordinary least squares model was used.[16]

The mortality by all causes in Portugal was obtained from the mortality tables of The Human Mortality Database.[17]

An annual discount of 5% was made for the costs and for the benefits (QALY, LY)[18] and was entered in the middle of each cycle.

Perspective of the Study and Guidelines Followed

The study was performed from the perspective of the Portuguese National Health Service (NHS) and included only direct health costs.[18]

The general guidelines for performing a cost-effectiveness analysis in Portugal were followed,[18] as well as the guidelines published by the Canadian Agency for Drugs and Technologies in Health,[19] the principles of good modeling practice of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR)[20] and the NICE recommendations.[21]

Costs Estimation

The cost estimation of a disease treated with a specific medicinal product is made by identifying and quantifying the healthcare resources involved and assigning them the respective unit costs. In this way, the mean costs for a "typical FL patient" were estimated. The healthcare resources costs used in the model are presented in euros (€) of 2014. The unit costs are set out in Table 1.

The annual costs were only taken into account from the randomization of the patients to the rituximab maintenance group or to the observation group in the PRIMA clinical trial. The following costs were analyzed: a) rituximab purchase and administration cost (estimation assuming the planned doses according to the summary of product characteristics of rituximab – base case scenario – or the actual doses received per patient in PRIMA clinical trial – sensitivity analysis[7]; b) adverse events (AE) costs according to the respective frequency of appearance in each treatment arm (rituximab or observation) of the PRIMA clinical trial[7] (for the estimation of severe or moderate AEs cost, the unit costs of the respective diagnosis related groups (DRG) were used; for mild AEs cost estimation an emergency consultation in Primary Care unit cost was used; both unit costs were obtained through an official Portuguese source)[22]; c) supportive care costs in all health states (except death); obtained from the health resources consumption estimation made by a Portuguese Onco-Hematologists panel and d) chemotherapy regimens costs used in the FL induction treatment.[23] Health resources consumption estimated by the Portuguese experts panel is presented in Appendix.

The cost of medicinal products exclusively used in hospitals were obtained using the National Authority of Medicines and Health Products – INFARMED, I.P. – price database,[23] public tender n.º 2013/6 from Serviços Partilhados do Ministério da Saúde[24] and the treatment costs were calculated assuming the prescribed doses in the PRIMA clinical trial[7] for a mean body weight of 71.15 kg and a mean height of 163 cm in accordance with the article by Sardinha *et al*[25] and a Portuguese population anthropometric study,[26] respectively. The FL patient cohort mean age (56 years) was established according to the mean age observed in the PRIMA clinical trial (Table 1).

Sensitivity Analysis

In order to check the model results stability and the consistency of the estimates made, deterministic sensitivity analyses were performed for the following variables; (i) type of statistical distribution (exponential, log-logistic, log-Normal, Gompertz or

Gamma); (ii) time horizon (20, 30 years and threshold analysis); (iii) re-using the left over medicinal product (that is, assuming no wastage); (iv) rituximab dose used in the PRIMA clinical trial; (v) ±20% of the supportive care costs in PFS and progression health states; (vi) ±20% of rituximab administration cost; (vii) ±20% of the AEs cost; (viii) ±10% of the health states utilities and finally (ix) discount rates of 0% and 6% for annual costs and benefits (Table 4).

A probabilistic sensitivity analysis was also performed using a Monte Carlo simulation in order to check the model robustness (Fig. 2).[27]

Results

The base case analysis was performed according to the premises indicated in Tables 1 and 2. Table 3 shows the base case result of deterministic analysis and also the probabilistic model results. The life years obtained with rituximab and observation in both PFS and progression health states are firstly presented. The difference between the two treatments options represent the life--years gained with rituximab. The same explanation serves for QALY results. Mean average total costs are also presented per patient treated with rituximab or under observation. These costs were obtained through the Markov model, based on the costs of health states (PFS, progression) and the transition probabilities between the states shown in Tables 1 and 2.

Table 3 – Base case results per patient*: deterministic and probabilistic analysis (€ of 2014)

Item	Deterministic			Probabilistic		
	Rituximab	Observation	Difference	Rituximab	Observation	Difference
Life years (LY)						
In PFS	6.472	5.395	1.077	6.475	5.395	1.080
In progression	0.512	0.887	-0.375	0.512	0.888	-0.376
Total	6.984	6.282	0.702	6.987	6.283	0.704
Quality adjusted life--years (QALYs)						
In PFS	5.544	4.612	0.932	5.546	4.612	0.934
In progression	0.318	0.550	-0.232	0.318	0.551	-0.233
Total	5.862	5.162	0.700	5.864	5.163	0.701
Mean total cost	€ 44,173	€ 36,708	€ 7,465	€ 44,173	€ 36,708	€ 7,465
Cost per life year gained		€ 10,634			€ 10,603	
Cost of one QALY gained		€ 10,664			€ 10,649	
Net monetary benefit		€ 13,603			€ 13,603	

PFS: progression-free survival.
* Weibull function. Time horizon: 10 years. Without re-using the vials (that is, considering wastage).

Cost Analysis

In the base case the mean cost per patient with rituximab maintenance was € 44,173 and € 36,708 in the observation group, with an incremental cost with rituximab of € 7,465 (Table 3).

Effectiveness Analysis

In the base case there were more life years (0.702) and more QALY (0.700) per patient with rituximab maintenance than with observation (Table 3).

Incremental Cost-Effectiveness

In the base case, for a time horizon of 10 years, the cost per LYG with the most efficacious treatment (maintenance with rituximab) was € 10,634 and the cost per QALY gained was € 10,664 (Table 3).

Sensitivity Analysis

The deterministic sensitivity analyses were performed according to changes in individual variables indicated in Table 4.

The sensitivity analysis results varied from € 6,821-11,478 per LYG and € 6,981-11,480 per QALY gained (annual discount rate of 0% and 6%, respectively, and a time horizon of 10 years). Maintenance with rituximab is cost-effective considering very short time horizons (even below the usual lifetime of a patient with FL) (Table 4).

The probabilistic sensitivity analysis confirmed the stability of the base case, with a cost per QALY gained of € 10,649. Rituximab was cost-effective in 100% of the simulations performed (Fig. 2). As can be observed from the incremental cost-effectiveness

Table 4 – Deterministic sensitivity analysis of the Markov model (€ of 2014)

Scenarios	Variations	Cost per LYG (€)	Cost per QALY gained (€)
Base case	-	10,634	
Sensitivity analysis (assumptions of the base case)			
With re-using the left over drug (without wastage)	-	11,709	
Supportive care costs in PFS and progression (mean)	-20% +20%	10,570 10,690	
Monthly costs of rituximab administration (€ 27.83)	-20% +20%	10,503 10,757	
Adverse events costs (mean)	-20% +20%	10,843 10,417	
Health states utilities (published values)	-10% +10%	- -	
Annual discount rates for costs and utilities (5%)	0% 6.0%	6,821 11,478	
Time horizon (10 years)	20 years 30 years Threshold: 5.5 years	6,805 6,507 29,191	
Other functions used to estimate the transition probabilities (Weibull)	Exponential Log-logistic Log-Normal Gompertz Gamma	10,601 10,850 12,881 10,601 12,153	

QALY: quality adjusted life-year; LYG: life year gained; PFS: progression-free survival.

acceptability curve, maintenance with rituximab would be cost-effective from an availability to pay of € 12,000 per QALY gained (Fig. 3).

Discussion

In accordance with the model results rituximab maintenance treatment of follicular lymphoma patients that respond to first line induction therapy is cost-effective in comparison with observation.

When assessing these results it must be taken into account that it is a theoretical model (that is, by definition, a simplified simulation of the reality) based, however, on the results of randomized clinical trials that directly compared the two options studied, with a non-pragmatic design. For this reason, the model validation by a panel of seven Portuguese Onco-Hematologists experts who estimated the resource use in the Portuguese clinical practice is of special importance, conferring reliability to its results. Thus, the results should be considered as valid estimations for Portuguese patients with the characteristics of those included in the analysis and may be useful as a decision-making tool in clinical practice.[6]

One aspect worth mentioning is that the health states utilities employed in the model were obtained from a study performed in the United Kingdom. Although the preferences for the health states can vary between countries due to cultural factors,[19] this risk is lower when comparing countries with similar socioeconomic level. In this respect, it should also be mentioned that in a study based on 83,000 evaluations of 44 health states by EuroQol (EQ-5D), performed in six European countries, a greater variability was observed between individuals than between countries.[28]

On the other hand, it must also be taken into account that using a Markov model it was possible to estimate, in a more "realistic" manner than with a pure deterministic model, the course of the disease over 10 years.[10] Likewise, it's worth to point out as a model "strength" the fact that the health resources and the AEs costs estimation were made using Portuguese official data sources[22-24] (e.g. DRGs) and that the utilities were obtained by means of adequate methodology from patients with FL.

In an attempt to minimize the model limitations conservative premises were taken for the base case scenario and deterministic and probabilistic analyses were performed; both confirmed the stability of the base case results.

Only one pharmacoeconomic study with rituximab maintenance treatment of FL patients that respond to first line induction therapy has been identified[9] and was carried out in the United Kingdom with same model used in the present study and with

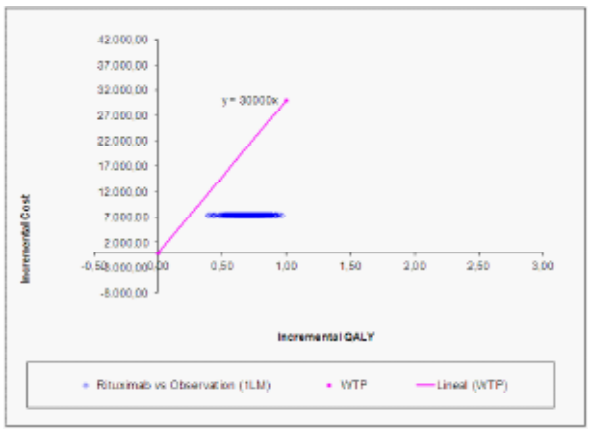

Figure 2 – Probabilistic analysis results (1,000 analyses; availability to pay € 30,000 per QALY gained)

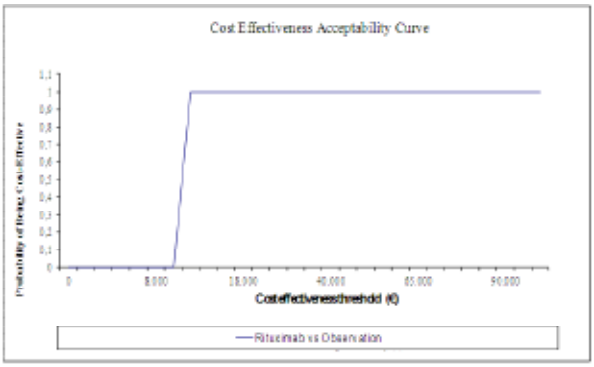

Figure 3 – Cost-effectiveness acceptability curve (the scheme with rituximab was cost-effective considering an availability to pay € 12,000). A cost-effectiveness probability of 100% for an availability to pay of € 30,000

similar results: cost per LYG and per QALY gained of £ 14,712 and £ 15,983, respectively (about € 16,600 and € 18,100, respectively). The incremental cost-effectiveness did not exceed £ 21,155 (about € 24,000) per QALY gained in the probabilistic analysis. The quantitative differences between the results must be due to the variations between the healthcare systems, as well as to the different unit costs of both countries.

Although the methodology followed in the present analysis is adequate, it would still be of interest to conduct pragmatic and randomized clinical trials that directly compare the efficacy, the utilities, the tolerability and the healthcare resources consumption related with the alternatives evaluated in order to confirm the results of this analysis. Meanwhile, in accordance with the results of the model, it can be concluded that, in comparison with observation, maintenance treatment of FL patients that respond to first line induction with rituximab (besides improving progression free survival) will give more quality-adjusted life years at a mean cost per QALY of € 10,674, thus it can be considered a cost-effective option.

Conflict of Interests

The authors state that there is no financial or personal relationship with other individuals or entities which may influence their work inappropriately.

Funding

Study performed with a research grant, with no restrictions, from Roche Farmacêutica Química, Lda., Portugal.

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Appendix – Health resources use estimation in Portugal (Delphi panel)

Treatment line	Resources	Monthly use per patient with Rituximab (min-max)	Monthly use per patient with Observation (min-max)
First line	Hematologist visit	0.44 (0.25-0.50)	0.31 (0.25-0.33)
	Complete blood count	0.44 (0.25-0.50)	0.31 (0.25-0.33)
	Thoraco-abdominal CT	0.10 (0.02-0.17)	0.09 (0.00-0.17)
	Full biochemical*	0.42 (0.25-0.50)	0.30 (0.00-0.33)
	Immunophenotype	0.08 (0.00-0.08)	0.08 (0.00-0.08)
	LDH	0.50 (0.00-0.50)	0.33 (0.00-0.33)
	Paracetamol (BSC)	0.71 (0.00-1.00)	0.00 (0.00-0.00)
Second line	Hematologist visit	0.43 (0.33-0.50)	0.33 (0.25-0.50)
	Complete blood count	0.43 (0.33-0.50)	0.33 (0.25-0.50)
	Thoraco-abdominal CT	0.11 (0.03-0.17)	0.10 (0.04-0.17)
	Full biochemical*	0.40 (0.00-0.50)	0.25 (0.08-0.33)
	Immunophenotype	0.08 (0.00-0.08)	0.08 (0.00-0.08)
	LDH	0.50 (0.00-0.50)	0.50 (0.00-0.50)
	Paracetamol (BSC)	0.71 (0.00-1.00)	0.00 (0.00-0.00)
Third line	Hematologist visit	0.42 (0.25-0.50)	0.36 (0.25-0.67)
	Complete blood count	0.42 (0.25-0.50)	0.36 (0.25-0.67)
	Thoraco-abdominal CT	0.11 (0.04-0.17)	0.12 (0.00-0.25)
	Full biochemical*	0.38 (0.25-0.50)	0.30 (0.00-0.33)
	Immunophenotype	0.08 (0.00-0.08)	0.08 (0.00-0.08)
	LDH	0.50 (0.00-0.50)	0.67 (0.00-0.67)
	Paracetamol (BSC)	0.57 (0.00-1.00)	0.00 (0.00-0.00)
Third line	**Treatment schemes**	**Rituximab first line %**	**Observation first line %**
	ESHAP	22.4% (0-23.7%)	0.2% (0-1.0%)
	R-ESHAP	4.4% (0-20.0%)	24.1% (0-40.0%)
	R-CHOP	4.2% (0-20.0%)	3.9% (0-20.0%)
	R-CVP	19.2% 0-60.0%)	23.0% 0-60.0%)
	R-FCM	7.3% (0-20.0%)	13.4% (0-30.0%)
	FCM	5.1% (0-30.0%)	0% (0-0%)
	R-ICE	3.4% (0-20.0%)	0% (0-0%)
	ICE	0% (0-0%)	3.1% (0-20.0%)
	R-Bendamustine	7.6% (0-25.0%)	11.0% (0-50.0%)
	Bendamustine	4.6% (0-25.0%)	0.3% (0-2.0%)
	Cyclophosphamide	5.1% (0-30.0%)	4.7% (0-30.0%)
	R-FC	4.2% (0-20.0%)	7.6% (0-38.0%)
	FC	5.8% (0-29.0%)	2.4% (0-15.0%)
	R-MINE	3.4% (0-20.0%)	6.3% (0-40.0%)
	MINE	3.4% (0-20.0%)	0% (0-0%)

BSC: best supportive care; CT: computed tomography; ESHAP: etoposide-methilprednisolone-cisplatin; FCM: fludarabine/cyclophosphamide/mitoxantrone; ICE: Ifosfamide/carboplatin/etoposide.; LDH: lactate dehydrogenase; max: maximum; min: minimum; MINE: mesna/ifosfamide/etoposide/mitoxantrone; R: rituximab; R-CHOP: rituximab + cyclophosphamide/doxorubicin/vincristine/ prednisone; R-CVP: rituximab + cyclophosphamide/vincristine/ prednisolone; R-ESHAP: rituximab + ESHAP; R-FC: rituximab + fludarabine/cyclophosphamide; R-FCM: rituximab + FCM; R-ICE: rituximab + ICE; R-MINE: rituximab + MINE.
* Creatinine, calcium, uric acid, etc.