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ORIGINAL ARTICLE

Cost-effectiveness of maintenance rituximab treatment after second line therapy in patients with follicular lymphoma in Sweden

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Abstract

Introduction. Rituximab has significantly improved the prognosis for patients with both indolent and aggressive non-Hodgkin's lymphoma. An economic evaluation was carried out to assess the cost-effectiveness in Sweden of rituximab as maintenance therapy for patients with follicular lymphoma in remission after second line therapy. *Materials and methods.* The incremental cost and effectiveness of rituximab maintenance therapy versus observation were evaluated in a health-state transition model. Primary effect measures were quality-adjusted life-years (QALY) and life-years gained (LYG). Model state transitions were calculated based on progression-free and overall survival data from the EORTC20981 trial. The analysis was made from the perspective of the healthcare provider, including direct medical costs presented in €, 2007 value. Effects and costs were discounted at a 3% annual rate. The stability of the base case results were tested in one-way and probabilistic sensitivity analyses. *Results.* The evaluation assessed rituximab maintenance therapy to be associated with an incremental cost per QALY gained of €12 600 and an incremental cost per LYG of €11 200. The average discounted life expectancy for patients on rituximab maintenance was 1.0 year longer than for patients on observation (5.96 vs. 4.94 years). Rituximab maintenance was associated with an additional 0.9 QALY, and total costs per patient were €11 500 higher in the treatment arm, compared to observation. *Discussion.* The results indicate that rituximab maintenance treatment after successful induction therapy for patients with relapsed/refractory follicular lymphoma in Sweden is cost-effective compared to observation.

Non-Hodgkin's lymphoma (NHL), a group of malignancies of the lymphoid system, ranks among the ten most common cancers in Sweden. There were 1 756 new cases of NHL, including CLL, diagnosed in Sweden in 2005 (3.4% of all cancer cases). Approximately 14% of NHL cases in Sweden are follicular lymphomas (FL) [1]. Follicular lymphoma is a cancer of the B-lymphocytes that occurs almost exclusively in adults. The median age of patients diagnosed with FL grade I-II in Sweden is approximately 63 years, 66 years for FL grade III. FL is an indolent disease with a median survival from diagnosis of 6 – 10 years. Exceptionally, patients presenting with FL in early stages may be cured with radiotherapy and/or chemotherapy, yet the overwhelming number of FL cases are incurable with any current treatment. Although treatment with single agent or combination chemotherapy can achieve complete or partial remissions in most patients, the clinical course is characterised by a continuous pattern of relapses requiring repeated treatment.

Until recently, no particular treatment approach clearly prolonged overall survival for patients with follicular lymphoma. However, in the past few years, rituximab (MabThera®, Rituxan®), a chimeric mouse/human anti-CD20 monoclonal antibody, has made a significant contribution to improving the outcome of patients with both aggressive and indolent NHL; the efficacy of rituximab in combination with chemotherapy has been demonstrated by several randomized trials [2–7]. Rituximab is licensed in the EU in combination with CVP chemotherapy for the first-line treatment of FL and in combination with CHOP chemotherapy for the treatment of patients with CD20-positive diffuse

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large B-cell lymphoma [8]. Moreover, four randomised trials have investigated rituximab maintenance therapy compared to 'observation'/'treatment delayed until relapse' in patients with relapsed/refractory FL in remission: EORTC20981, GLSG-FCM, SAKK, and LYM-5 [5,9–11]. All the trials showed that there is an overall benefit from rituximab maintenance therapy. Patients in the trials had received different induction therapies: CHOP, R-CHOP, Rituximab 375 mg/m^2, FCM, and R-FCM. The EORTC20981 study included 167 relapsed/refractory FL patients in each treatment arm of the maintenance phase; the other three studies included less than 50 patients in each treatment arm. The EORTC20981 trial [5,12] was thus found to offer the best evidence base for assessment for a cost-effectiveness evaluation. The trial was designed to investigate the benefit of rituximab added to CHOP chemotherapy for the treatment of relapsed/refractory CD20-positive follicular lymphoma as well as to assess the efficacy of rituximab maintenance therapy in prolonging the duration of response and consisted of two randomisations. At the second randomisation, patients in the rituximab maintenance group received 375 mg/m^2 of rituximab once every three months until disease progression or relapse, or for a maximum period of 24 months, while patients in the observation group received no active therapy until disease progression. At disease progression, the patients were eligible for any post-protocol treatment deemed appropriate by the treating physician. The observation arm of the clinical study was thus similar to the prevailing treat-on-relapse approach for patients that have responded to induction therapy; which makes clinical data from EORTC20981 appropriate for determining the cost-effectiveness of rituximab maintenance therapy compared to current clinical practice. The aim of this economic evaluation is to assess the cost-effectiveness, in Sweden, of rituximab added in the maintenance settings for patients with relapsed/refractory FL in remission after second-line therapy.

Material and methods

The economic evaluation is based on a previously developed disease model, programmed in Microsoft Excel®, evaluating the incremental cost and effectiveness of rituximab maintenance over observation [13]. The model is a health-state transition model of Markov type with three health states: progression-free (PF), progressive disease (PD) and death. Patients are followed through the health states in monthly cycles over a period of 30 years, in order to capture the full life expectancy of patients. The model structure is presented in Figure 1.

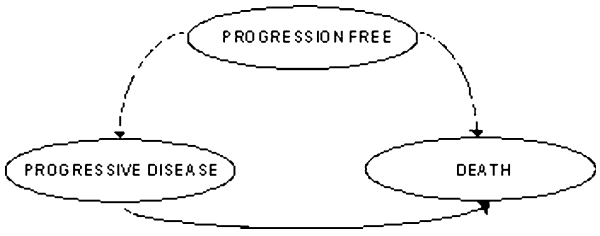

Figure 1. Model design.

The hypothetical patient cohort in the economic evaluation is a representation of the population enrolled and randomised in the maintenance phase of EORTC20981, assessed to reflect the patient population likely to be eligible for maintenance therapy in a clinical setting.

The primary endpoints of the economic evaluation are the incremental costs per quality-adjusted life year (QALY) gained and the incremental cost per life year gained (LYG) over the lifetime of the patients. The analysis was made from the perspective of the healthcare provider, i.e. the economic evaluation was based on direct health care costs. Costs are presented in €, 2007 value (€1 = SEK9.25). One-way sensitivity analyses were performed to test the stability of the results and identify the input parameters with particularly influence on the results. A probabilistic sensitivity analysis was also performed to assess the joint stability of the model parameters. Costs and effects were discounted at a 3% annual rate [14].

Clinical data

Progression-free survival (PFS) and overall survival (OS) were based on data from EORTC20981. Median PFS from second randomisation in EORTC20981 was 51.5 months in the rituximab arm versus 14.9 months in the observation arm (HR: 0.40, $p < 0.001$). OS was also significantly longer in the rituximab arm compared to observation: 85% at three years in the rituximab arm versus 77% in the observation arm (HR: 0.52, $p = 0.011$) [5,12]; the superior effect was consistent across all subgroups evaluated regardless of risk level at study entry, type of induction regimen, and response level to induction regimen. For the first two years in the model, which was approximately the median duration of follow-up in EORTC20981, Kaplan Meier (KM) data from the trial was used. Thereafter, extrapolation of PFS and OS to the 30-year horizon of the economic model was achieved by fitting a Weibull distribution to the survival data observed during the EORTC20981 trial. The hazards in the model reflect the differences in terms of progression-free and overall survival observed in EORTC20981.

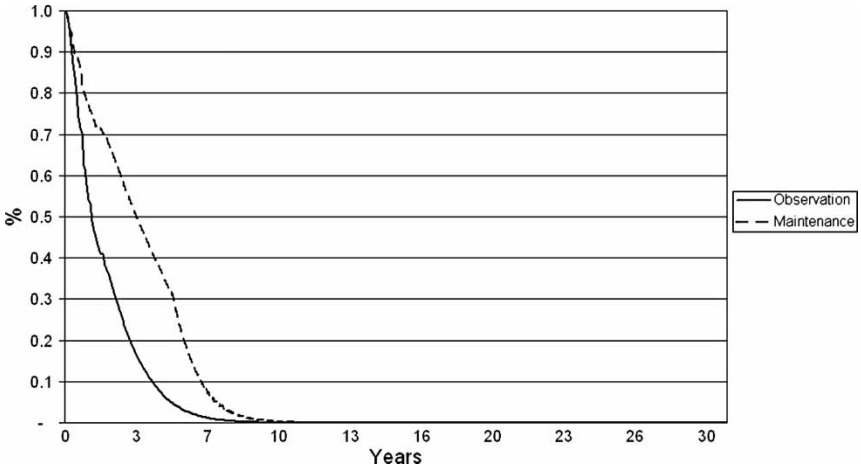

Figure 2. Extrapolation of progression-free survival data.

Figures 2 and 3 show the results of the extrapolation in the model.

During the maintenance phase, the incidence of grade 3 and 4 adverse events were 37% in the rituximab arm versus 23% in the observation arm while the incidence of serious adverse events were 13% in the rituximab arm versus <1% in the observation arm. The incidence of serious adverse events and the costs they were estimated to incur are presented in Table II.

Cost data

In addition to the cost of the maintenance therapy in itself, direct medical cost consequences of the maintenance therapy include the clinical benefit in terms of reduction in relapses as well as the cost of treating adverse events. Drug costs were Swedish national prices from the National Corporation of Swedish Pharmacies [15], unit costs for out-patient visits and medial procedures were based on prices from the university hospitals of Malmö and Uppsala [16,17], Inpatient diagnosis-related costs were derived from the national inpatient case-costing database [18] and expert opinion.

Cost for rituximab treatment, including costs for drugs and administration were calculated based on the drug utilisation recorded in the EORTC20981 trial. The average cost per patient on maintenance therapy (drug cost and administration) is presented in Table I.

Costs of resource use and hospitalisation for serious adverse events were based on the national inpatient case-costing database [18] and further validated by an expert panel [19]. Costs of adverse event are presented in Table II. The average cost per patient due to serious adverse events was estimated to €587 in the rituximab maintenance arm and €23 in the observation arm. However, due to the longer time of follow-up in patients receiving rituximab and the open label design of EORTC20981, there is a potential bias against rituximab in the estimation of adverse events.

During the maintenance phase, on average 1.6 non-serious adverse events per patient occurred in

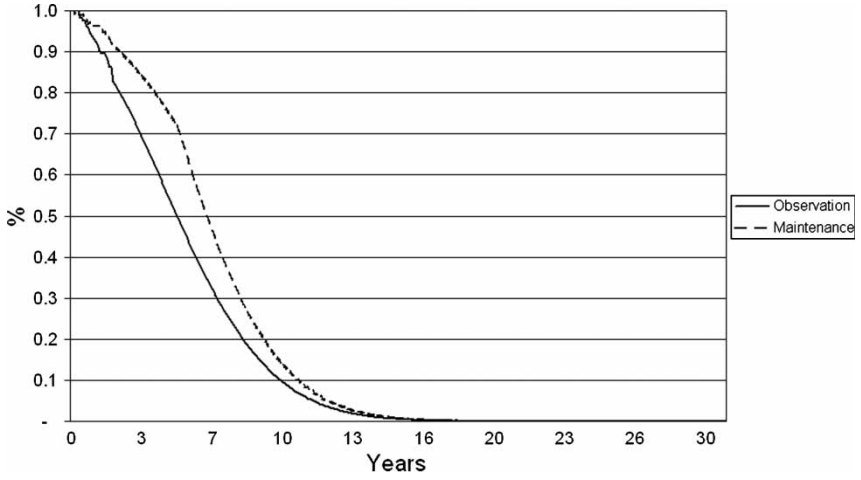

Figure 3. Extrapolation of overall survival data.

Table I. Cost of maintenance therapy.

Parameter	
Rituximab cost per 100 mg vial (€)	285
Rituximab dose (mg/m^2)	375
Rituximab dispensed dose (mg)	759
Rituximab drug costs per dose (€)	2 159
Mean number of rituximab doses per patient (SD = 2.74)	5.9
Total rituximab drug costs per patient* (€)	12 637
Mean cost per administration (Out-patient visit Haematology) (€)	90
Total rituximab administration cost per patient* (€)	526
Total cost of maintenance therapy (€)	13 163

*Total costs have been discounted as the maintenance therapy encompassed two years.

the rituximab arm and 1.4 events per patient occurred in the observation arm. It was assessed that half of the non-serious adverse events would lead to a medical visit (€225). The total average cost per patient due to non-serious adverse events was estimated to €180 in the rituximab arm and €162 in the observation arm.

Treatment costs upon relapse were included to reflect the cost of therapies likely to be received after disease progression in the trial. Treatment costs upon relapse are based on post-protocol treatments recorded in EORTC20981, and were estimated separately for maintenance and observation, as the type of treatment a patient would receive could depend on whether he/she had received maintenance therapy in second line (Table III). The unit costs of treatments received upon relapse were weighted according to the EORTC20981 post-protocol treatment distribution. The average costs per patient per relapse treatment episode were estimated to €11 249 for the rituximab group and €11 117 for the observation group. It was estimated that the patients would experience a relapse every two years on average, as long as they remained alive, due to the continuous pattern of relapses that is characteristic for follicular lymphoma; the time interval of two years was based on the time to first progression observed in the EORTC20981. The cost of relapse treatment was thus divided into a monthly cost over two year periods, incurred by patients in the progressive disease state of the model.

Cost of routine management/surveillance for patients in the progression-free state (during maintenance therapy) was assessed to consist of a physician visit (€225) every three months, while it was assumed that patients with progressive disease would visit their physician monthly.

Quality of life data

Utility values (where 1 is considered as one year of perfect health and 0 as dead) were taken from a British study that used the EQ-5D instrument to assess the quality of life in patients with follicular lymphoma [20]. The study presented utility values of 0.805 (n = 132) for progression-free and 0.618 for

Table II. Cost of serious adverse events during the maintenance phase.

Rituximab maintenance	Unit cost (€)	No of SAEs	% of SAEs
Blood Cell Disorders	3 729	1	3.3%
Minor Infections (including Immune Disorders)	2 892	2	6.7%
Bronchopneumonia, w/o cc	2 700	6	20.0%
Septicaemia	6 983	1	3.3%
Other Gastrointestinal or Metabolic Disorders	1 814	3	10.0%
Kidney or Urinary Tract Infections, w/o cc	2 324	2	6.7%
Nervous System Disorders	2 554	2	6.7%
Other unassigned condition	2 458	1	3.3%
Pulmonary Embolis, w/o cc	4 435	1	3.3%
Skin, Musculoskeletal, or Connective Tissue Disorders	9 992	1	3.3%
Intermediate Pain Procedures	2 685	1	3.3%
Heart Failure or Shock, w/o cc	3 893	2	6.7%
Ischaemic Heart Disease without intervention, w/o cc	3 263	1	3.3%
Upper Respiratory Tract Disorders	2 267	1	3.3%
Acute Liver Disorders	2 715	1	3.3%
Acute Myocardial Infarction, w/o cc	4 529	2	6.7%
Asthma, w/o cc	1 724	1	3.3%
Malignant Breast Disorders, w/o cc	3 718	1	3.3%
Average cost per event	3 267	30	100.0%
Average cost per patient (n = 167)	587		
Observation	**Unit cost (€)**	**No of SAEs**	**% of SAEs**
Heart Failure or Shock, w/o cc	3 893	1	100.0%
Average costs per patient *(n = 167)*	23		

Table III. Unit costs of treatments received upon relapse [15,18–20].

Treatment	Cost (€)	Proportion of patients receiving therapy	
		Rituximab	Observation
Chemotherapy	3 547	0.63	0.44
Rituximab single agent	13 533	0.05	0.23
Rituximab chemotherapy combination	16 540	0.06	0.09
Radiotherapy	3 008	0.09	0.12
Allogeneic stem cell transplantation (ASCT)	84 089	0.05	0.04
Autologous stem cell transplantation (ASCT)	39 259	0.05	0.03
Rituximab+ASCT	74 520	0.00	0.01
Chemoradiotherapy	6 554	0.01	0.02
Interferon maintenance	10 366	0.03	0.00
Other	0	0.02	0.04
Average total costs per patient for treatment upon relapse		€11 249	€11 117

progressive disease (n = 33). The utility values were directly applied to the PF and PD health states in the model.

Results

The results of the base-case analysis are presented in Table IV. The economic evaluation resulted in an incremental cost per QALY gained with rituximab maintenance treatment of €12 600. The incremental cost per LYG was estimated to €11 200. The average discounted life expectancy in the rituximab group was 1.0 year longer than in the observation group (5.96 vs. 4.94 years). Rituximab maintenance was associated with an additional 0.9 QALY compared to the observation group. Total costs per patient were €11 500 higher in the rituximab arm compared to the observation arm. The simulation model hence indicates that maintenance therapy with rituximab for patients in remission after second line treatment of follicular lymphoma in Sweden is cost-effective compared to observation.

Table V shows the average total discounted cost per patient in the simulation, including treatment of adverse events, treatment costs upon relapse, and routine management. In the rituximab maintenance arm, the total cost per patient amounted to €39 600, while the total cost per patient in the observation group was calculated to €28 200. The cost of maintenance therapy and the treatment costs upon relapse are the greatest cost drivers, while the difference in costs between the two treatment arms of €11 500 was principally due to the cost and administration of maintenance therapy.

The stability of the base-case result was tested in sensitivity analyses (Table VI). Decreasing the duration of follow-up and treatment benefit in the model affected the results, yet the incremental cost-effectiveness ratios remained within the acceptable range also under assumptions of a duration of follow-up limited to four years (base-case 30 years) and a duration of treatment benefit of two years (base-case five years), which nevertheless indicates the importance of assessing the long-term clinical consequences of the investigated treatment. Extrapolation of progression-free and overall survival by using a log-logistic distribution lead to a somewhat smaller incremental cost-per-effect measure; the log-logistic regression model resulted in longer estimated life-length of patients than the Weibull regression model and the survival advantage of maintenance therapy was thus extended. Results were robust to 50% changes in cost parameters.

A probabilistic sensitivity analysis was performed to test the stability of the deterministic (base-case) results by assessing the joint uncertainty of the underlying clinical, quality-of-life and cost parameters. The covariate parameters in the Weibull

Table IV. Base case results

	Result per QALY gained			Result per life-year gained		
	Rituximab maintenance	Observation	Incremental	Rituximab maintenance	Observation	Incremental
Total cost (€)	39 617	28 156	11 461	39 617	28 156	11 461
Total effect (QALY/LYG)	4.29	3.38	0.91	5.96	4.94	1.02
ICER* (Δcost/Δeffect)	€12 584/QALY			€11 187/LYG		

* Incremental cost-effectiveness ratio

Table V. Cost data (€).

	Rituximab maintenance	Observation	Incremental
Study drug costs (including administration)	13 163	0	13 163
Adverse events	767	186	582
Treatment costs upon relapse	15 399	17 776	−2 377
Routine management	10 288	10 195	94
Total cost	39 617	28 156	11 461

regression model were varied according to an inverse normal distribution. The clinical data on adverse events and post protocol treatments were drawn from beta distributions, and quality-of-life data were varied following a trimmed normal distribution; with parameter variation based on the original data from the clinical trial and the quality-of-life study. Cost data were varied within an estimated range according to triangular or linear distributions.

The probabilistic sensitivity analyses showed that rituximab maintenance therapy was more effective with an incremental effectiveness of more than 0.37 QALY in 100% of the performed simulations. The incremental cost of rituximab maintenance treatment did not exceed €25 400 in any case (Figure 4). The average incremental effect in the probabilistic analysis was 0.9 QALY and the average incremental cost was €11 500.

The acceptability curve derived from the probabilistic sensitivity analysis (Figure 5) demonstrates that rituximab maintenance treatment would incur a cost per QALY gained of less than €25 400 in 100% of the simulated cases. The willingness-to-pay (WTP) threshold for which a treatment is considered cost effective is generally considered to be approximately €54 000 (SEK 500 000) in Sweden [21]. This indicates that the calculated base-case cost-effectiveness results are stable and that rituximab maintenance therapy can be considered a cost-effective treatment for patients with FL in remission after second line therapy.

Discussion

The cost-effectiveness of rituximab maintenance therapy in patients with relapsed/refractory follicular lymphoma who have responded to induction therapy has previously not been assessed in a Swedish setting. The results of the economic modelling indicate that rituximab maintenance therapy is a cost effective intervention, with an incremental cost

Table VI. One-way sensitivity analysis.

Description of variable tested	Value in base case	Description of sensitivity analysis	Value in sensitivity analysis	Incremental cost per QALY gained (€)	Incremental cost per LYG (€)
Base case				*12 584*	*11 187*
Duration of follow-up in the model	30 years	Range of values	4 years	24 836	30 346
			7 years	12 798	12 349
			10 years	12 551	11 360
			50 years	12 584	11 187
Duration of treatment benefit	5 years	Observation arm hazards applied for PFS and OS in both arms from the end of the treatment benefit	2 years	29 124	29 460
			3 years	19 170	18 520
			10 years	10 619	8 508
			30 years	10 789	8 339
Distribution used for extrapolation of PFS & OS	Weibull	Log-logistic	Log-logistic	9 904	8 552
Unit cost of non serious adverse event (€)	112	Value halved	56	12 574	11 179
		Value doubled	225	12 604	11 205
Adverse events	Included	Excluded	–	11 946	10 620
Unit cost per line of treatment upon relapse (€)	OBS = 11 117 RIT = 11 249	Double cost in OBS arm only	OBS = 22 234 RIT = 11 249	RIT dominant	RIT dominant
		Double cost in RIT arm only	OBS = 11 117 RIT = 22 499	29 492	26 219
		Double cost in both arms	OBS = 22 234 RIT = 22 499	9 975	8 867

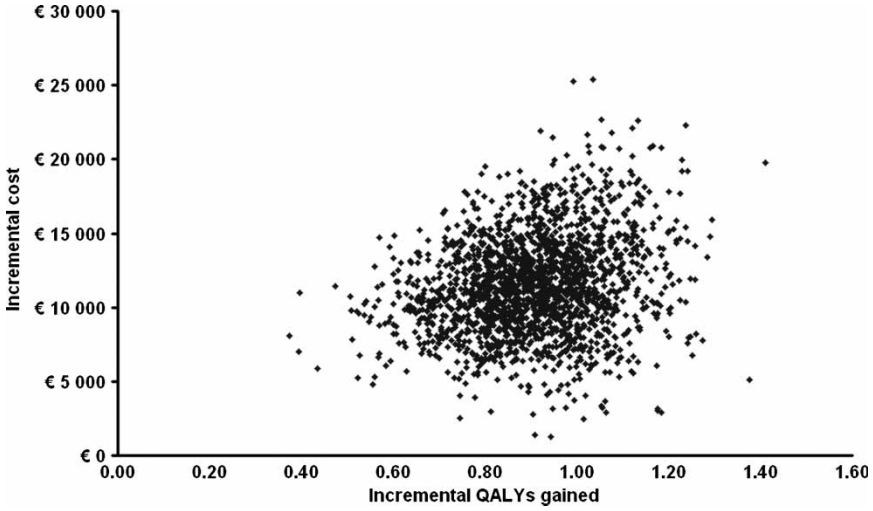

Figure 4. Probabilistic sensitivity analysis.

per QALY gained over observation of €12 600. For comparison, an Italian study from 2007, likewise based on the EORTC20981 trial and similar model design, assessed the cost effectiveness of rituximab maintenance to €11 100 per QALY gained [13].

The aim of a health economic model is to model clinical practice and clinical effects as accurately as possible, nevertheless, a model is a simplification of reality and although the most valid clinical data available is in many cases data from clinical trials, these data may not always be completely comparable to clinical practice. For example, the assessment of treatment received upon relapse, based on data from the EORTC20981 trial, might not be completely equivalent to what would be given to Swedish patients today since clinical practice might have changed since the trial was conducted. However, due to the small difference in average costs of treatment received upon relapse between the two treatment arms in the study, it is unlikely that variations in treatment upon relapse would greatly affect the cost difference between treatment arms. Likewise, the costs of adverse events in the economic model were based on clinical expert estimates and data from the Swedish inpatient case-costing database and not empirically verified, but as shown in the sensitivity analysis, variations in costs of adverse events had limited impact on the results of the analysis.

The economic evaluation does not include indirect costs. In Sweden approximately 55% of patients are under 65 years of age at diagnosis of FL. Thus, including cost of production loss would have had a certain influence on the model results. Since all patients experienced relapses the difference between the treatment arms would have been limited, but

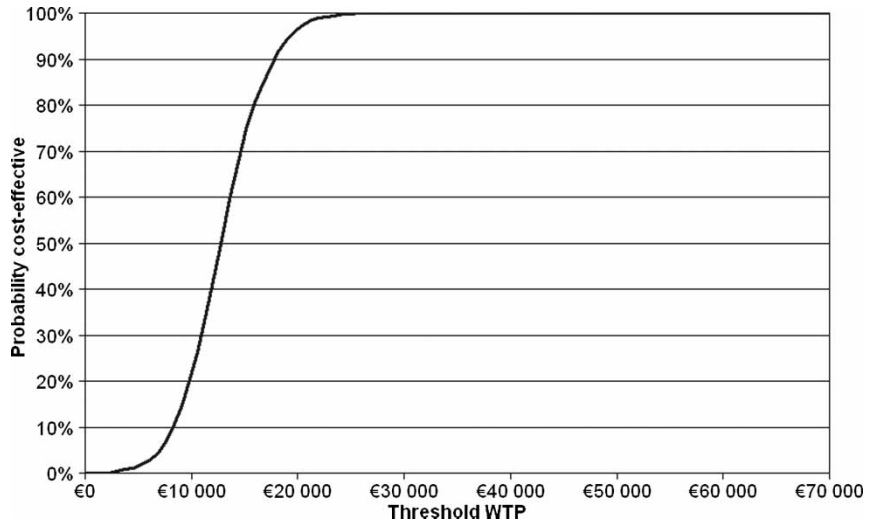

Figure 5. Acceptability curve.

assumable in favour of ritixumab since patients treated with rituximab had a prolonged time to relapse/refraction. The greatest indirect cost is generally the cost of mortality and since survival was prolonged for patients treated with rituximab in the present simulation, it can be considered a conservative approximation not to include indirect costs in the analysis. The significant clinical benefit for rituximab maintenance therapy demonstrated in the EORTC20981 trial reassures the stability of the cost-effectiveness results.

Acknowledgements

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