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Comparing the Cost-Effectiveness of Rituximab Maintenance and Radioimmunotherapy Consolidation versus Observation Following First-Line Therapy in Patients with Follicular Lymphoma

Qiushi Chen, BS[1], *Turgay Ayer, PhD*[1], *Loretta J. Nastoupil, MD*[2,3], *Adam C. Rose, MD*[2], *Christopher R. Flowers, MD, MS*[2,3,*]

[1]*H. Milton Stewart School of Industrial & Systems Engineering, Georgia Institute of Technology, Atlanta, GA, USA;* [2]*Department of Hematology and Medical Oncology, School of Medicine, Emory University, Atlanta, GA, USA;* [3]*Winship Cancer Institute, Emory University, Atlanta, GA, USA*

ABSTRACT

Background: Phase 3 randomized trials have shown that maintenance rituximab (MR) therapy or radioimmunotherapy (RIT) consolidation following frontline therapy can improve progression-free survival for patients with follicular lymphoma (FL), but the cost-effectiveness of these approaches with respect to observation has not been examined using a common modeling framework. **Objectives:** To evaluate and compare the economic impact of MR and RIT consolidation versus observation, respectively, following the first-line induction therapy for patients with advanced-stage FL. **Methods:** We developed Markov models to estimate patients' lifetime costs, quality-adjusted life-years (QALYs), and life-years (LYs) after MR, RIT, and observation following frontline FL treatment from the US payer's perspective. Progression risks, adverse event probabilities, costs, and utilities were estimated from clinical data of Primary RItuximab and MAintenance (PRIMA) trial, Eastern Cooperative Oncology Group (ECOG) trial (for MR), and First-line Indolent Trial (for RIT) and the published literature. We evaluated the incremental cost-effectiveness ratio for direct comparisons between MR/RIT and observation. Model robustness was addressed by one-way and probabilistic sensitivity analyses. **Results:** Compared with observation, MR provided an additional 1.089 QALYs (1.099 LYs) and 1.399 QALYs (1.391 LYs) on the basis of the PRIMA trial and the ECOG trial, respectively, and RIT provided an additional 1.026 QALYs (1.034 LYs). The incremental cost per QALY gained was $40,335 (PRIMA) or $37,412 (ECOG) for MR and $40,851 for RIT. MR and RIT had comparable incremental QALYs before first progression, whereas RIT had higher incremental costs of adverse events due to higher incidences of cytopenias. **Conclusions:** MR and RIT following frontline FL therapy demonstrated favorable and similar cost-effectiveness profiles. The model results should be interpreted within the specific clinical settings of each trial. Selection of MR, RIT, or observation should be based on patient characteristics and expected trade-offs for these alternatives.

Keywords: cost-effectiveness, follicular lymphoma, lymphoma, maintenance, non-Hodgkin lymphoma, radioimmunotherapy, rituximab.

Introduction

Follicular lymphoma (FL) is the most common subtype of indolent non-Hodgkin's lymphoma in the United States (US) [1,2], accounting for approximately 20% of 580,000 prevalent non-Hodgkin's lymphoma cases in 2011 [1,3]. Although FL in limited stage is curable with standard radiation therapy [4], most of the patients with FL are diagnosed with advanced-stage disease [5,6], which remains incurable. FL management also produces an economic burden to patients and the US society, with an annual cost ranging from $20,000 to $36,000 per patient [7].

This cost is associated with substantial patient benefit. In the past few decades, the median overall survival (OS) of patients with FL significantly improved from 11 years to 18 years, following advances in effective therapies and supportive care [8]. In the modern era, chemotherapy and rituximab plus chemotherapy (R-chemotherapy) have commonly been used for previously untreated patients with advanced-staged FL. In current practice, however, there is no single approach that has become the standard for first-line treatment [9]. Advanced-stage FL typically produces a course of recurrent remissions and relapses with reducing response rate, remission duration, and health-related quality of

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* *Address correspondence to:* Christopher R. Flowers, 1365 Clifton Road, N.E. Building B, Suite 4302, Emory University, Atlanta, GA 30322. E-mail: crflowe@emory.edu.

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life (HRQOL) along with subsequent treatments. As a result, in the absence of curative therapies, many efforts have focused on extending the duration of the first remission to postpone subsequent treatment and to help patients maintain a higher HRQOL.

Maintenance with rituximab (MR) and radioimmunotherapy (RIT) consolidation are two approaches aiming at such improvement. Rituximab, an anti-CD20 monoclonal antibody with favorable toxicity profile, has been a major therapeutic advance for FL treatment in the last several decades. It has been used as a single agent, in combination with chemotherapy, or as maintenance therapy in newly diagnosed and relapsed patients [10]. Patients undergoing MR following the induction therapy continue to receive rituximab for an additional 2 years. RIT uses radiation-labeled anti-CD20 antibody to deliver radiation to malignant cells. It first showed a high response rate in patients with relapsed FL [11] and was later applied as a consolidation strategy following first-line treatment.

For untreated patients with FL, MR and RIT consolidation also have demonstrated clinical benefit. MR for 2 years has been shown to significantly improve the progression-free survival (PFS, i.e., time from randomization to disease progression or death) and the rate of complete response (i.e., complete disappearance of all evidence of disease [12]) in the randomized Primary RItuximab and MAintenance (PRIMA) and Eastern Cooperative Oncology Group (ECOG) trials [13,14]. RIT consolidation following induction chemotherapy or R-chemotherapy also showed similar efficacy results in the randomized First-line Indolent Trial (FIT) [15,16]. Each approach demonstrated an improvement in PFS over observation without producing significant differences in patients' HRQOL [14,17]. As a result, MR and RIT consolidation have been approved for use in the frontline setting since 2011 and 2009, respectively. A randomized phase 2 trial, ZAR2007, will provide a head-to-head comparison between MR and RIT following first-line induction with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) therapy [18]. Preliminary results from this trial showed similar partial response to the complete response conversion rate, no significant difference in OS, and a superior 3-year PFS for MR. As indicated above, however, studies comparing frontline strategies in FL may require more than a decade of follow-up to demonstrate difference in OS. These data remain immature, and longer follow-up is awaited for a more comprehensive comparison of survival benefits for the two approaches.

In clinical practice, MR is commonly used. An analysis based on the largest prospective study of FL in the United States, the National LymphoCare Study, showed that among 1186 patients who received frontline rituximab-based induction therapy, 46% received MR [19]. However, because a single dose of RIT consolidation may provide comparable efficacy to MR for 2 years, RIT could be preferred in some circumstances although it is much less commonly used [20]. For MR and RIT consolidation, it is unclear whether the additional costs are worth the benefits when compared with observation. In this study, we evaluated and compared the economic impact of MR and RIT consolidation versus observation, respectively, following the first-line induction therapy for patients with advanced-stage FL.

Methods

General Approach

We developed three separate Markov models on the basis of three phase 3 randomized clinical trials, respectively: one model compared RIT with observation following the first-line induction therapy based on FIT [15,16], and two models compared 2-year MR with observation based on the PRIMA trial [14] and the ECOG trial [13], respectively. We refer to each model using the corresponding trial name throughout the article. There existed differences in patient characteristics and treatment regimens across the trials (Table 1). For example, the

Table 1 – Patients and treatment regimens in randomized trials.

Characteristics	ECOG1496		PRIMA		FIT	
	MR*	OBS	MR†	OBS	RIT‡	OBS
N	115	113	505	513	204	205
Age (y)						
Median (range)	58 (30-84)§	54 (30-84)§	57 (26–79)	55 (22–84)	55 (29–78)	53 (27–74)
≥60, n (%)	47 (41)	38 (34)	176 (35)	180 (35)	58 (28)	48 (24)
Advanced stage (3/4), n (%)	73 (64)‖	72 (64)‖	459 (91)	459 (89)	202 (99)	199 (97)
Sex: male, n (%)	59 (51)	62 (55)	270 (53)	263 (51)	97 (48)	103 (50)
FLIPI score, n (%)						
Low	23 (26)	24 (27)	106 (21)	110 (21)	56 (37)	62 (43)
Intermediate	32 (36)	32 (36)	183 (36)	187 (36)	58 (39)	54 (37)
High	33 (38)	33 (37)	215 (43)	216 (42)	36 (24)	30 (21)
B symptoms, n (%)	22 (19)	34 (30)	160 (32)	156 (30)	46 (23)	42 (21)
Induction therapy, %	CVP	CVP	R-CHOP: 76 R-CVP: 22 R-FCM: 3	R-CHOP: 75 R-CVP: 22 R-FCM: 3	Chlorambucil: 10 CVP/COP: 26 CHOP: 31 CHOP-like: 15 FLU-comb: 5 R-comb: 13	Chlorambucil: 9 CVP/COP: 26 CHOP: 28 CHOP-like: 15 FLU-comb: 6 R-comb: 16

CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; comb, combination; CVP/COP, cyclophosphamide, vincristine, and prednisone; ECOG, Eastern Cooperative Oncology Group; FCM, fludarabine with mitoxantrone and cyclophosphamide; FIT, First-line Indolent Trial; FLIPI, the Follicular Lymphoma International Prognostic Index; FLU, fludarabine; MR, rituximab maintenance; OBS, observation; PRIMA, Primary RItuximab and MAintenance; R, rituximab; RIT, radioimmunotherapy.

* Rituximab 375 mg/m^2 once a week for 4 wk every 6 mo for 2 y.

† Rituximab 375 mg/m^2 every 8 wk for 2 y.

‡ Rituximab 250 mg/m^2 on day −7 and day 0 followed on day 0 by 90Y-ibritumomab tiuxetan 14.8 MBq/kg; maximum of 1184 MBq.

§ The range is for all FL patients in the trial.

‖ Only stage 4 reported.

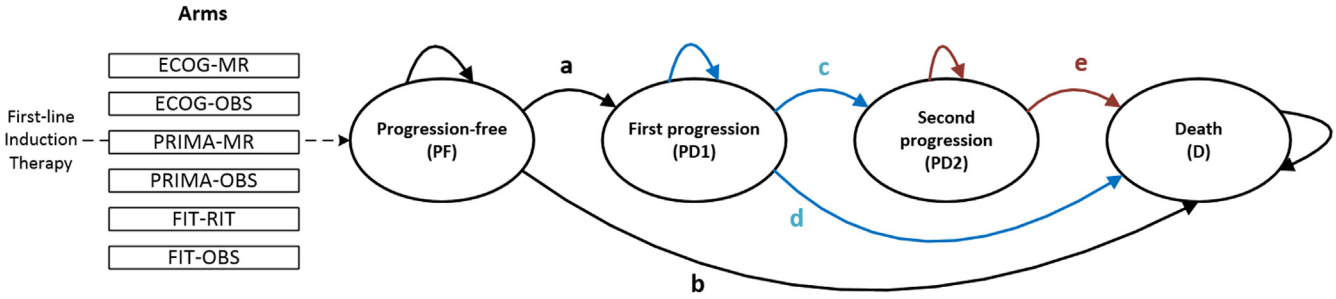

Fig. 1 – Markov model. Description and data sources: a: PFS for each arm (i.e., MR/RIT/OBS), source: PRIMA/ECOG/FIT trial. b: OS for each arm (i.e., MR/RIT/OBS), source: PRIMA/ECOG/FIT trial and the US life table. c: PFS after first progression, source: EROTC20981 trial (the second randomization, OBS arm without MR). d: OS after first progression, source: EROTC20981 trial. e: OS after second progression, source: Rummel et al. [25]. ECOG, Eastern Cooperative Oncology Group; EROTC, European Organisation for Research and Treatment of Cancer; FIT, First-line Indolent Trial; MR, rituximab maintenance; OBS, observation; PRIMA, Primary RItuximab and Maintenance; RIT, radioimmunotherapy.

induction therapy was chemotherapy in the ECOG trial and for most patients in the FIT, but it was R-chemotherapy in the PRIMA trial. In addition, the regimens of MR differed slightly between PRIMA and ECOG trials. The differences in induction therapy affected patients' outcomes. Therefore, it was not appropriate to perform an indirect comparison between MR and RIT using the data from the trials with different induction therapies. Instead, we built three separate models, where each model inherited the specific clinical settings from the corresponding clinical trial.

In each Markov model, we evaluated the lifetime cost and total quality-adjusted life-years (QALYs) for MR, RIT, and observation following first-line induction therapy, respectively. Health states defined for the clinical course included 1) before first progression, 2) first progression, 3) second progression, and 4) death (Fig. 1). The structure for the models was determined on the basis of the typical disease course of a patient with FL, in line with previously published models for FL treatment [21,22]. The model simulated outcomes for patients on the completion of first-line induction therapy. During the long disease course of FL, patients' age also in part affects their survival outcomes. Because FL is commonly diagnosed in patients with a wide range of age, to better project the outcomes for the FL population beyond the narrow age distribution of the clinical trial, we sampled the initial age of each patient in the microsimulation from the distribution of age at diagnosis of FL from the Surveillance, Epidemiology, and End Results database between 1992 and 2009 [23].

The Markov model simulated transitions between health states in each model cycle, which represented 1 month. We considered up to three lines of treatment. Patients with relapsed FL were assumed to receive R-CHOP/CHOP therapy without MR in the second-line treatment [24] and bendamustine with rituximab (BR) in the third-line treatment [25]. For first- and second-line treatments, patients could remain in the same health state, progress to the next line of treatment, or die, with estimated probabilities based on clinical data. Following the third-line treatment, only risks of death were considered. We applied half-cycle corrections [26] for model parameters to address the possibility that state transitions could occur at any time point within each cycle.

Costs were associated with each health state. We adopted the US payer's perspective, and therefore considered direct medical costs, which captured the consumption of all resources directly attributable to the treatment strategy. Direct nonmedical costs (e.g., transport costs) and indirect costs (e.g., loss of productivity) were not considered in the model. All cost estimates were converted to 2013 US dollars on the basis of the Consumer Price Index in the medical care category [27]. We followed standard recommendations for conducting health economic evaluation and discounted the clinical outcomes and costs at the annual rate of 3% [28]. Each model was developed in Treeage Pro 2011, and statistical analyses were performed in R.

Progression Risk and Mortality

The probabilities of the first progression in each model were estimated on the basis of PFS curves in the published randomized trials [13,14,16]. Risks of the second progression were estimated on the basis of the PFS curve of the observation group in the European Organisation for Research and Treatment of Cancer phase III trial EORTC 20981 for patients with relapsed FL (i.e., R-CHOP/CHOP therapy without MR) [22,24]. A further analysis based on this trial has shown that the end points were not significantly different across different prior therapies, which enabled us to safely assume that transition probabilities after the second-line treatment were identical for each arm. To estimate the monthly risk of progression, we used Engauge Digitizer to retrieve the data points from each PFS curve plot, and fitted parametric survival models using these data points. We considered Weibull, log-logistic, and Gompertz distributions for survival models. To maintain consistency between the arms for comparisons, we selected a common survival distribution that demonstrated good fit for all PFS and OS curves of treatment and observation arms in each trial. In the final analysis, we used log-logistic distributions for first- and second-line treatments and Gompertz distributions for the third-line treatment. Other survival distributions were tested in sensitivity analyses. We applied Bayes' rule to derive the monthly risk of progression, as a conditional probability of progression in 1 month given that the patient has not progressed yet. Risk estimates beyond the follow-up time of clinical trials were extrapolated from the fitted survival model. Because differences in survival outcomes continued to separate beyond the median follow-up time, we assumed the duration of treatment effect to be 6 years and risks of progression or death in MR and RIT arms to be the same as those in observation arms after 6 years, which is in line with a previously published model of FL treatment [22].

Mortality risk was defined as the maximum of cause-specific mortality and other-cause mortality at each cycle. The cause-specific mortality before the first progression was estimated on the basis of OS curves for each arm in the PRIMA trial, the ECOG trial, and FIT, and cause-specific mortalities of second and third-line treatments were derived from the OS curves of CHOP/R-CHOP treatment [24] and BR treatment [25] for relapsed FL, respectively. Other-cause mortality for each age group was estimated from the US life tables [29].

Utility and Cost Estimates

The HRQOL for MR and RIT consolidation has been assessed in clinical studies separately. We used the health utility estimates from the published literature. The utilities were estimated as 0.88

for MR and observation in the PRIMA and ECOG models [22,30,31] and 0.84 for RIT and 0.83 for observation in the FIT model [17] before the first progression, 0.79 after the first progression, 0.62 after the second progression, and 0 for the death state [22,30–32].

Only direct costs were considered in this study, including drug costs, administration costs, monitoring costs, and adverse event costs. The drug costs for MR and RIT consolidation were calculated on the basis of dosing for the regimens in each trial, while no drug costs were incurred in the observational arm. The infusion dosages for FL treatments were computed on the basis of a body surface area with a mean value of 1.835 m^2 [22]. The wholesale acquisition cost [33] was used for the unit cost of each drug. The cost estimate for the second-line treatment was based on an established practice pattern for relapsed FL previously described in a published FL modeling study [22], and the cost of third-line treatment was based on the bendamustine and rituximab regimen [25].

Unlike RIT, which has only one-time drug infusion, MR and second- or third-line treatment extend for more than one model cycle and require multiple drug administrations (e.g., 2 years for MR, 18 weeks for R-CHOP/CHOP, and 16 weeks for BR). We divided the total costs of drugs and administration by the complete treatment duration, and allocated the same amount in each month over the treatment periods. This way, only the resources used and the corresponding costs occurred to that point were attributed to individual patients in the models because patients in the model could die or progress to the next line of treatment during any model cycle as in clinical practice.

We estimated the cost of grade 3/4 adverse events on the basis of our clinical coauthors' expert opinion in the management strategies for each adverse event. We assumed that patients with grade 3/4 infection/febrile neutropenia were hospitalized and others were managed as outpatients. The cost of hospitalization included inpatient physician service fees and hospital reimbursement based on the length of stay diagnosis-related group (DRG) code corresponding to the adverse event [34]. For other hematological adverse events, the cost included outpatient visit cost and the cost of the materials for the adverse event management (see Appendix 1 for details in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2014.12.017). For each treatment strategy, the cost of each adverse event was obtained by multiplying the incidence and the unit cost for each type of adverse event.

Drug administration and adverse event costs were calculated using the Medicare physician fee schedule for 2013 [35]. Each medical service performed by a physician is associated with a specific Health Care Procedure Coding System code and/or the Current Procedure Terminology code. For each procedure, we determined its relative value units on the basis of the Health Care Procedure Coding System/Current Procedure Terminology code from the Centers of Medicare & Medicaid Services database [35], and then computed the outpatient physician service cost on the basis of relative value units [34]. Monitoring costs included the costs of blood tests and physician visits every 3 months, and costs of computed tomography scans every 6 months, which were independent of the treatment arm and the current line of treatment (Table 2).

Sensitivity Analysis

We conducted sensitivity analyses to evaluate the robustness of the model and to address the uncertainty in parameter estimation. Ranges and distributions of the parameters used in sensitivity analysis are summarized in Table 2. Utilities were varied over their 95% confidence intervals. For each procedure, physician fees were adjusted by different geographic pricing cost index adjustment factors, and the ranges of physician fees were determined by the lowest and highest costs in the Centers of Medicare & Medicaid Services fee schedule. Similarly, to define the ranges for DRG-based hospital reimbursement, we computed the DRG rate for each of 3500 providers in the United States [34] and found the lowest and the highest DRG rates. Drug costs were varied within ±10% of their baseline values. We acknowledge that the treatment duration effect may be conservative for ECOG and FIT models because these trials have a longer follow-up time. Therefore, we varied the duration from the minimum follow-up time of 3 years to lifetime in the sensitivity analysis.

In univariate sensitivity analysis, we examined the effect of each parameter on incremental cost-effectiveness ratios (ICERs) separately. In probabilistic sensitivity analysis (PSA), parameters were sampled simultaneously according to their sampling distributions. We followed recommended distributions based on parameter types, and assumed lognormal distribution for cost and beta distribution for utility and incidence of adverse events (Table 2) [36]. We ran 10,000 replications for the PSA.

In secondary sensitivity analyses examining the robustness of the model structure, the models were evaluated on the basis of different fitted survival distributions. In addition, we compared MR and observation in a combined model, in which we aggregated the fitted PFS and OS curves of each arm using the weighted log-relative-risk method [37], and estimated risks on the basis of aggregated survival curves. Other model parameters were combined by taking the average of the estimates from multiple studies weighted by the sample size of each study.

Results

In primary analyses, effectiveness and costs were compared within each clinical trial. Based on the PRIMA study, MR therapy provided 7.64 QALYs at a cost of $112,780 compared with 6.55 QALYs at a cost of $68,855 for the observation arm. Based on the ECOG study, MR therapy provided 6.51 QALYs at a cost of $124,405 compared with 5.11 QALYs at a cost of $72,066 for the observation arm. Based on FIT, RIT therapy provided 6.60 QALYs at a cost of $115,011 compared with 5.57 QALYs at a cost of $73,098 for the observation arm. The ICERs for MR were $40,335 and $37,412/QALY gained in the PRIMA study and the ECOG study, respectively, and the ICER for RIT was $40,851/QALY gained based on FIT. Our model also estimated total projected life-years (LYs) without quality adjustment and provided the effectiveness and cost estimates by treatment period as summarized in Table 3.

Results of univariate sensitivity analyses are presented in the tornado diagrams (Fig. 2). The most influential common factors for all three models included utility before first progression in the maintenance/consolidation arm or the observation arm in each trial, drug cost for MR and RIT, duration of treatment effect, and discount factor. In the PSA, the incremental cost and effectiveness from 10,000 samples are shown in the scatterplots for each trial (see Appendix 2 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2014.12.017). The results of the PSA are also presented in the cost-effectiveness acceptability curve (Fig. 3). The cost-effectiveness acceptability curves showed that MR and RIT consolidation is cost-effective compared with observation at $50,000/QALY willingness-to-pay threshold, with probability 58%, 74%, and 62% in the PRIMA, ECOG, and FIT model, respectively. At a willingness-to-pay threshold of $100,000/QALY, the probabilities become 79%, 92%, and 84%, respectively. The models were also shown to be robust to the input risk estimates. The results produced similar ICER estimates when different fitted survival models were used (see Appendix 3 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2014.12.017). In the combined model, MR provided an additional 1.13 QALYs (1.15 LYs) at the incremental cost of $46,234 compared with observation and the ICER was $40,956 per QALY gained.

Table 2 – Estimates, ranges, and distributions of model parameters.

Model input	Value	Minimum	Maximum	Distribution for PSA
BSA	1.835 m^2			
Cost of rituximab maintenance ($)[*]				
PRIMA regimen (12 doses)	54,588			
PRIMA regimen: monthly cost	2,275	2,047	2,502	Lognormal ($\mu = 7.73$, $\sigma = 0.10$)[†]
ECOG regimen (16 doses)	72,784			
ECOG regimen: monthly cost	3,033	2,729	3,336	Lognormal ($\mu = 8.01$, $\sigma = 0.10$)
Cost of radioimmunotherapy consolidation ($)	46,566	41,910	51,223	Lognormal ($\mu = 10.74$, $\sigma = 0.10$)
Cost of second-line treatment ($) [22]				
Average cost of second-line therapies	46,504	41,854	51,155	Lognormal ($\mu = 10.74$, $\sigma = 0.10$)
Cost of third-line treatment ($)				
Bendamustine + rituximab (four courses)	45,433	40,891	49,977	Lognormal ($\mu = 10.72$, $\sigma = 0.10$)
Administration cost ($)[‡]				
Monthly administration cost of chemotherapy[§]				
PRIMA regimen	88	62	117	Lognormal ($\mu = 4.43$, $\sigma = 0.30$)
ECOG regimen	117	82	155	Lognormal ($\mu = 4.72$, $\sigma = 0.30$)
Radioimmunotherapy administration cost				
Radiopharmaceutical therapy, radiolabeled-monoclonal antibody, IV (CPT: 79403)	190	151	234	Lognormal ($\mu = 5.22$, $\sigma = 0.22$)
Monitoring cost ($)				
CT scans: chest/abdomen/pelvis (CPT: 72129, 74160, 72193)	828	598	1,083	Lognormal ($\mu = 6.68$, $\sigma = 0.29$)
Laboratory tests [50]	76	68	84	Lognormal ($\mu = 4.33$, $\sigma = 0.10$)
Other procedures cost ($)				
Outpatient physician visits (CPT: 99213)	50	43	66	Lognormal ($\mu = 3.88$, $\sigma = 0.23$)
Inpatient physician visits				
First visit (CPT: 99222)	135	117	179	
Subsequent visits (CPT: 99232)	70	62	94	
Discharge visit (CPT: 99238)	71	61	93	
Blood transfusion (CPT: 36430)	35	23	47	
Adverse event cost ($)[‖]				
Anemia	1,881	1,826	1,910	Lognormal ($\mu = 7.54$, $\sigma = 0.02$)
Neutropenia	3,066	2,758	3,384	Lognormal ($\mu = 8.02$, $\sigma = 0.10$)
Febrile neutropenia/infection	11,566	7,092	27,656	Lognormal ($\mu = 9.07$, $\sigma = 0.76$)
Thrombocytopenia	1,086	593	1,139	Lognormal ($\mu = 6.96$, $\sigma = 0.23$)
Incidence of adverse events				
PRIMA study				
MR arm, neutropenia	0.040	0.020	0.060	Beta ($a = 3.84$, $b = 92.16$)[¶]
MR arm, febrile neutropenia/infection	0.040	0.020	0.060	Beta ($a = 3.84$, $b = 92.16$)
OBS arm, neutropenia	0.010	0	0.040	Beta ($a = 0.99$, $b = 98.01$)
OBS arm, febrile neutropenia/infection	0.010	0	0.040	Beta ($a = 0.99$, $b = 98.01$)
MR and OBS arm, anemia, thrombocytopenia	0.005	0	0.040	Beta ($a = 0.03$, $b = 5.50$)
ECOG study				
MR arm, neutropenia	0.030	0.020	0.050	Beta ($a = 3.88$, $b = 125.45$)
MR arm, febrile neutropenia/infection	0.010	0	0.020	Beta ($a = 3.96$, $b = 392.04$)
OBS arm, neutropenia	0.010	0	0.040	Beta ($a = 0.99$, $b = 98.01$)
OBS arm, febrile neutropenia/infection	0.010	0	0.040	Beta ($a = 0.99$, $b = 98.01$)
MR and OBS arm, anemia, thrombocytopenia	0.005	0	0.040	Beta ($a = 0.03$, $b = 5.50$)
FIT				
RIT arm, neutropenia	0.667	0.400	0.700	Beta ($a = 136.04$, $b = 67.92$)
RIT arm, febrile neutropenia/infection	0.079	0.040	0.120	Beta ($a = 3.68$, $b = 42.95$)
RIT arm, anemia	0.034	0.018	0.228	Beta ($a = 4.36$, $b = 123.93$)
RIT arm, thrombocytopenia	0.608	0.400	0.650	Beta ($a = 82.15$, $b = 52.96$)
OBS arm, neutropenia	0.025	0	0.040	Beta ($a = 2.71$, $b = 105.63$)
OBS arm, febrile neutropenia/infection	0.024	0	0.040	Beta ($a = 2.20$, $b = 89.30$)
OBS arm, anemia	0	0	0.040	Beta ($a = 0.03$, $b = 5.50$)
OBS arm, thrombocytopenia	0	0	0.040	Beta ($a = 0.03$, $b = 5.50$)
Utility				
No progression, MR	0.88	0.81	0.95	Beta ($a = 18.96$, $b = 2.59$)
No progression, RIT	0.84	0.77	0.91	Beta ($a = 23.04$, $b = 4.39$)
No progression, OBS				
PRIMA study	0.88	0.81	0.95	Beta (a = 18.96, b = 2.59)
FIT study	0.83	0.76	0.90	Beta ($a = 23.90$, $b = 4.90$)
Combined	0.87	0.79	0.94	Beta ($a = 18.55$, $b = 2.86$)

continued on next page

Table 2 – *Continued*

Model input	Value	Minimum	Maximum	Distribution for PSA
After the first progression	0.79	0.72	0.86	Beta ($a = 26.75$, $b = 7.11$)
After the second progression	0.62	0.48	0.76	Beta ($a = 7.45$, $b = 4.57$)
Discount factor	0.03	0	0.05	-
Effective horizon (mo)	72	36	Until progression	-

BSA, body surface area; CPT, Current Procedure Terminology; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; FIT, First-line Indolent Trial; MR, rituximab maintenance; OBS, observation; PRIMA, Primary RItuximab and MAintenance; PSA, probabilistic sensitivity analysis; RIT, radioimmunotherapy; WAC, wholesale acquisition cost.

* WAC for the unit cost of the drug [33], values of drug costs varied by ±10% in one-way sensitivity analysis, and lognormal distributions were used in the PSA.

† Parameters of lognormal distribution are determined on the basis of mean and standard deviation (SD) of the variable (SD is estimated on the basis of half of the range of parameter value).

‡ For the cost estimates of procedures, we used the national payment amount (i.e., geographic pricing cost index = 1), conversion factor for 2013 was $34.02, and all the cost estimates were based on the CY 2013 PFS final rule [35].

§ Chemotherapy administration takes 3 h for the first course and 2 h for subsequent courses.

‖ See Appendix 1 for details.

¶ Parameters of Beta distribution are determined on the basis of the point estimate and the sample size in the original study.

Discussion

MR and RIT consolidation are two commonly considered strategies following the first-line induction therapy for patients with FL to improve patients' response and survival without disease progression. In this study, we evaluated the long-term benefits and costs of these two treatments, MR and RIT, compared with observation. In our model, both MR and RIT showed that patients' total QALYs were improved at reasonable costs, with the estimated ICERs below the threshold of $50,000 per additional QALY. We assessed the uncertainty in the model results and demonstrated moderate confidence of cost-effectiveness for MR and RIT, with about 60% likelihood of an ICER of $50,000/QALY or less and 80% of an ICER of $100,000/QALY or less.

Different induction therapies may affect the projected effectiveness of MR, RIT, and observation. Given that most of the patients in FIT received frontline chemotherapy without rituximab whereas all patients in the PRIMA trial received R-chemotherapy (Table 1), the two studies did not have similar PFS and OS in their observation arm. We observed that survival curves for the RIT arm of the FIT model were comparable with those for the observation arm of the PRIMA model, which led to similar model outputs: 6.60 QALYs (8.48 LYs) and 6.55 QALYs (8.28 LYs) for each arm, respectively. This was validated externally by a recent comparison between R-CHOP followed by observation and CHOP followed by RIT (I^{131} tositumumab) in a phase 3 randomized clinical trial (S0016) [38]. This study showed that both strategies had outstanding PFS and OS but there was no

Table 3 – Base-case result.

Model output	PRIMA model		ECOG model		FIT model	
	MR	OBS	MR	OBS	RIT	OBS
LYs						
Before first progression	6.239	4.520	4.751	2.451	5.042	3.204
Total LYs	9.376	8.277	8.136	6.744	8.481	7.447
QALYs						
Before first progression	5.491	3.977	4.181	2.157	4.235	2.659
Total QALYs	7.643	6.553	6.505	5.107	6.597	5.572
Costs ($)						
Adverse event	600	161	222	161	3,683	354
Before first progression	63,015	9,620	71,515	5,160	61,028	6,979
First progression to second progression	26,612	31,463	28,216	35,630	28,913	35,184
After second progression	23,154	27,772	24,675	31,276	25,071	30,937
Total	112,781	68,856	124,406	72,066	115,012	73,099
Incremental values						
LYs		1.099		1.391		1.034
QALYs		1.089		1.399		1.026
Costs ($)		43,925		52,339		41,913
Incremental cost-effectiveness ratios						
Incremental cost per LY gained		39,968		37,627		40,535
Incremental cost per QALY gained		40,335		37,412		40,851

ECOG, Eastern Cooperative Oncology Group; FIT, First-line Indolent Trial; LY, life-year; MR, rituximab maintenance; OBS, observation; PRIMA, Primary RItuximab and MAintenance; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; RIT, radioimmunotherapy.

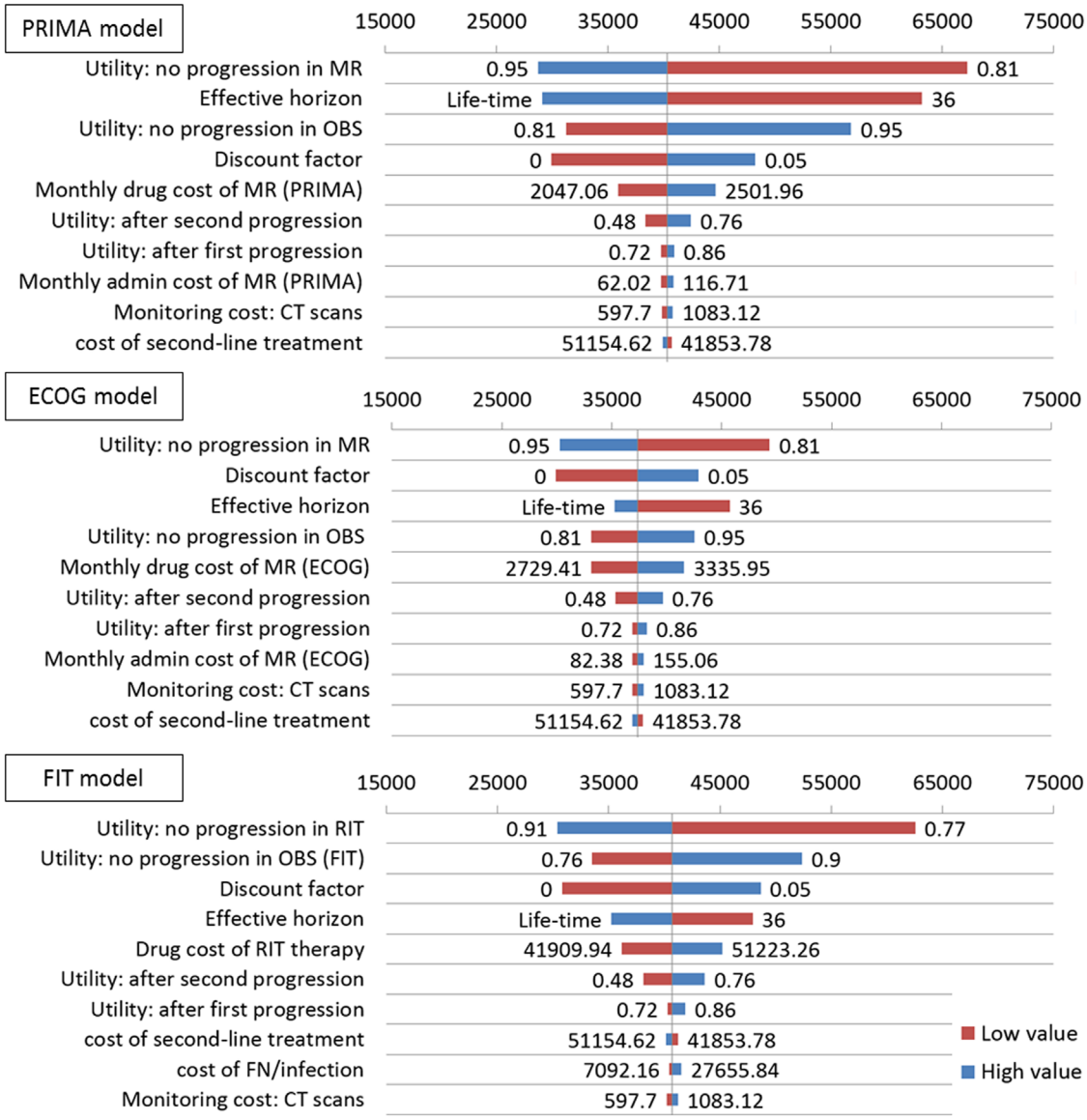

Fig. 2 – Tornado diagrams of most influential variables to ICERs. CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; FIT, First-line Indolent Trial; ICER, incremental cost-effectiveness ratio; MR, rituximab maintenance; OBS, observation; PRIMA, Primary RItuximab and Maintenance; RIT, radioimmunotherapy.

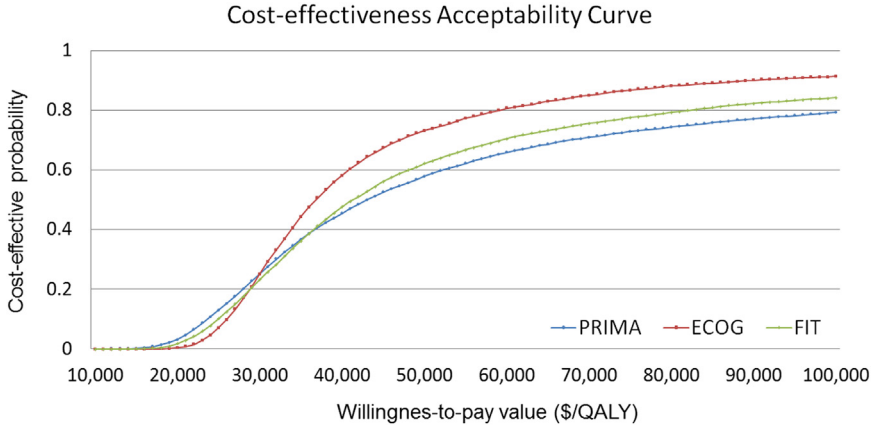

Fig. 3 – Cost-effectiveness acceptability curves. ECOG, Eastern Cooperative Oncology Group; FIT, First-line Indolent Trial; PRIMA, Primary RItuximab and Maintenance; QALY, quality-adjusted life-year.

significant difference between the two groups ($P = 0.11$ comparing 2-year PFS).

The cost before first progression was mainly driven by drug cost in each trial. According to the wholesale acquisition cost, RIT costs approximately $46,000, and a full course of MR costs approximately $54,000 (12 courses) in the PRIMA trial and $72,000 (16 courses) in the ECOG trial. Adverse event costs were more significant for RIT than for MR and observation, due to the high incidences of anemia and thrombocytopenia following RIT consolidation. This finding is in line with the high incidence of adverse events reported in a series of phase 2 studies [39–44]. However, patients in the observation arms progressed earlier, leading to higher costs after first progression. These models help to describe and quantify to what extent the additional costs of treatment and adverse events following frontline therapy for FL are counterbalanced by the benefit of maintaining more prolonged remissions.

Sensitivity analyses showed that the utility before first progression following MR or RIT was the most important factor in all three models, which suggests that improving patients' HRQOL following MR or RIT consolidation could make these approaches more cost-effective. Limited data, however, exist on the HRQOL associated with MR or RIT based on small cohorts in trials: a UK study [31] and the FIT study. Additional assessments of the HRQOL for patients with FL in the first remission would be warranted to better understand the robustness of these findings. Moreover, the duration of treatment benefit also played an important role in the cost-effectiveness of MR and RIT. The models also showed that treatment can become more cost-effective if the treatment can prolong the duration of remission and reduce the risk of disease-related mortality. The cost-effectiveness of MR in the PRIMA model in this study was in line with a published cost-effectiveness analysis [22]. The estimates of total QALYs for both arms were slightly lower in our model, which could be attributed to differences in the initial age distribution and the fitted distribution of survival curves.

Our study has limitations. First, there are differences in induction therapies and patient characteristics across trials, which may influence the model parameters, such as risk and utility estimates. This also limited our ability to combine study results and to directly compare the ICERs of MR and RIT. Second, the utilities for patients in MR and observation in PRIMA and ECOG models were estimated from a separate UK study [31] because health utility estimates are not available from the original trials. More comprehensive estimates of utilities for the general population would further improve the accuracy and robustness of the model. Third, we did not differentiate the health states on the basis of response to the treatment owing to lack of data concerning response-specific utility and survival estimates. In addition, in clinical practice, disease progression does not necessarily indicate an immediate treatment for patients with FL. Therefore, time-to-next-treatment is preferable to PFS in representing the transition to the next line of treatment. Time-to-next-treatment data were not available, however, for the ECOG trial or relapsed FL studies.

Our analyses showed that the cost-effectiveness of MR and RIT was comparable to that of other treatments for advanced-stage FL, which replaced an older standard of care. For example, the ICERs were $20,000 to 30,000 per QALY gained for first-line R-chemotherapy regimens compared with chemotherapy alone [30,45,46], for first-line BR compared with R-chemotherapy [47], and for MR compared with observation for relapsed FL [32,48]. Despite differences in model settings, costs, and health systems between countries, these studies revealed a similar magnitude of ICERs of these treatment strategies for indolent lymphoma. Based on our model results, MR and RIT consolidation following first-line induction therapy for patients with advanced-stage FL also appeared to be reasonably cost-effective approaches.

However, the favorable cost-effectiveness profile of MR and RIT does not imply a uniform approach of selecting treatments in the general population. For an individual patient, selection of either approach or observation should depend on individual patient characteristics, such as performance status. The risks of severe adverse events induced by RIT (such as cytopenias) should also be considered, although these have a limited effect on the cost-effectiveness of RIT. Moreover, the length of treatment may also affect the decision. MR requires repeated treatment over 2 years, whereas RIT requires only one drug infusion, which may be more accessible to patients in certain circumstances [49].

In summary, we used the same modeling framework and consistent parameter estimates to evaluate the cost-effectiveness of MR and RIT compared with observation following frontline treatment for patients with FL. Both strategies showed favorable cost-effectiveness profile for these approaches to prevent FL disease progression when compared with observation following frontline therapy. Although differences in induction therapies in these three trials should be noted when the ICERs of maintenance/consolidation therapies are compared, this work provides the most comprehensive assessment to date comparing the cost-effectiveness of these strategies. Future analyses comparing these approaches would benefit from more direct assessment of the HRQOL during the period of MR or observation following frontline therapy and long-term follow-up data from randomized trials directly comparing MR and RIT consolidation.

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Supplemental Materials

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REFERENCES

[1] Chan W, Armitage J, Gascoyne R, et al. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. Blood 1997;89:3909–18.
[2] Swerdlow SH. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC Press, 2008.
[3] Howlader N, Noone AM, Krapcho M, et al., eds. SEER Cancer Statistics Review, 1975-2011. Bethesda, MD: National Cancer Institute, 2014.
[4] Hoppe BS, Hodgson DC, Advani R, et al. ACR Appropriateness Criteria®: localized nodal indolent lymphoma. Oncology (Williston Park) 2013;27:786–94.
[5] Friedberg J, Huang J, Dillon H, et al. Initial therapeutic strategy in follicular lymphoma (FL): an analysis from the National LymphoCare Study (NLCS). Presented at: ASCO Annual Meeting Proceedings, June 2-6, 2006, Atlanta, GA.
[6] Freedman A. Follicular lymphoma: 2012 update on diagnosis and management. Am J Hematol 2012;87:988–95.
[7] Gleeson M, Carolina R, Danese M, et al. Cost of follicular lymphoma (FL) in Medicare patients. Presented at: ASCO Annual Meeting Proceedings, May 30-June 3, 2008, Chicago, IL.
[8] Tan D, Horning SJ. Follicular lymphoma: clinical features and treatment. Hematol Oncol Clin North Am 2008;22:863–82.
[9] van Oers MHJ, Kersten MJ. Treatment strategies in advanced stage follicular lymphoma. Best Pract Res Clin Haematol 2011;24:187.
[10] Flowers CR, Armitage JO. A decade of progress in lymphoma: advances and continuing challenges. Clin Lymphoma Myeloma Leuk 2010;10:414–23.
[11] Witzig TE, Gordon LI, Cabanillas F, et al. Randomized controlled trial of yttrium-90–labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory

low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. J Clin Oncol 2002;20:2453–63.
[12] Cheson B. New response criteria for lymphomas in clinical trials. Ann Oncol 2008;19:iv35–8.
[13] Hochster H, Weller E, Gascoyne RD, et al. Maintenance rituximab after cyclophosphamide, vincristine, and prednisone prolongs progression-free survival in advanced indolent lymphoma: results of the randomized phase III ECOG1496 study. J Clin Oncol 2009;27:1607–14.
[14] Salles G, Seymour JF, Offner F, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. Lancet 2011;377:42–51.
[15] Morschhauser F, Radford J, Van Hoof A, et al. 90Yttrium-ibritumomab tiuxetan consolidation of first remission in advanced-stage follicular non-Hodgkin lymphoma: updated results after a median follow-up of 7.3 years from the International, Randomized, Phase III First-Line Indolent trial. J Clin Oncol 2013;31:1977–83.
[16] Morschhauser F, Radford J, Van Hoof A, et al. Phase III trial of consolidation therapy with yttrium-90–ibritumomab tiuxetan compared with no additional therapy after first remission in advanced follicular lymphoma. J Clin Oncol 2008;26:5156–64.
[17] Gondek K, Shah S, Bischof-Delaloye A, et al. Health-related quality of life in patients with advanced-stage follicular lymphoma receiving consolidation with 90Y-ibritumomab tiuxetan (Zevalin(R)) of first remission: results from the randomized phase 3 First-Line Indolent Trial (FIT). ASH Annu Meet Abstr 2007;110:3319.
[18] Canales MA, Dlouhy I, Briones J, et al. A randomized phase II study comparing consolidation with a single dose of 90Y ibritumomab tiuxetan (Zevalin®)(Z) vs. maintenance with rituximab (R) for two years in patients with newly diagnosed follicular lymphoma (FL) responding to R-CHOP: preliminary results at 36 months from randomization. Blood 2013;122:369.
[19] Nastoupil LJ, Sinha R, Byrtek M, et al. The use and effectiveness of rituximab maintenance in patients with follicular lymphoma diagnosed between 2004 and 2007 in the United States. Cancer 2014;120:1830–7.
[20] Illidge TM. Radioimmunotherapy of lymphoma: a treatment approach ahead of its time or past its sell-by date? J Clin Oncol 2010;28:2944–6.
[21] Soini EJ, Martikainen JA, Vihervaara V, et al. Economic evaluation of sequential treatments for follicular non-Hodgkin lymphoma. Clin Ther 2012;34:915–925. e2.
[22] Hornberger J, Chien R, Friedmann M, et al. Cost-effectiveness of rituximab as maintenance therapy in patients with follicular non-Hodgkin lymphoma after responding to first-line rituximab plus chemotherapy. Leuk Lymphoma 2012;53:2371–7.
[23] Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) research data (1973-2011). In: SSB, ed., Surveillance Research Program. National Cancer Institute, DCCPS, April 2014, based on the November 2013 submission. Bethesda, MD: National Cancer Institute, 2014.
[24] van Oers MHJ, Klasa R, Marcus RE, et al. Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-Hodgkin lymphoma in patients both with and without rituximab during induction: results of a prospective randomized phase 3 intergroup trial. Blood 2006;108:3295–301.
[25] Rummel MJ, Al-Batran SE, Kim S-Z, et al. Bendamustine plus rituximab is effective and has a favorable toxicity profile in the treatment of mantle cell and low-grade non-Hodgkin's lymphoma. J Clin Oncol 2005;23:3383–9.
[26] Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. Medical Decis Making 1993;13:322–38.
[27] Archived Consumer Price Index detailed report information. 2013. Available from: http://www.bls.gov/cpi/cpi_dr.htm. [Accessed September 1, 2013].
[28] Drummond MF, Sculpher MJ, Torrance GW, et al. Methods for the Economic Evaluation of Health Care Programmes (3rd ed.). New York, NY: Oxford University Press, 2005.
[29] Arias E. United States life tables, 2007. Natl Vital Stat Rep 2011;59:1–60.
[30] Papaioannou D, Rafia R, Rathbone J, et al. Rituximab for the first-line treatment of stage III–IV follicular lymphoma (review of Technology Appraisal No. 110): a systematic review and economic evaluation. Health Technol Assess 2012;16:1366–5278.
[31] Wild D, Walker M, Pettengell R, et al. Utility elicitation in patients with follicular lymphoma. Value Health 2006;9:A294.
[32] Deconinck E, Miadi-Fargier H, Le Pen C, et al. Cost effectiveness of rituximab maintenance therapy in follicular lymphoma. Pharmacoeconomics 2010;28:35–46.
[33] Curtiss FR, Lettrich P, Fairman KA. What is the price benchmark to replace average wholesale price (AWP)? J Manag Care Pharmacy 2010;16:492–501.
[34] Tumeh JW, Moore SG, Shapiro R, Flowers CR. Practical approach for using Medicare data to estimate costs for cost-effectiveness analysis. Expert Rev Pharmacoecon Outcomes Res 2005;5:153–62.
[35] Medicare physician fee schedule. 2013. Available from: http://www.cms.gov/apps/physician-fee-schedule/. [Accessed September 1, 2013].
[36] Briggs AH, Weinstein MC, Fenwick EA, et al. Model parameter estimation and uncertainty analysis: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force Working Group–6. Med Decis Making 2012;32:722–32.
[37] Earle CC, Wells GA. An assessment of methods to combine published survival curves. Med Decis Making 2000;20:104–11.
[38] Press OW, Unger JM, Rimsza LM, et al. Phase III randomized intergroup trial of CHOP plus rituximab compared with CHOP chemotherapy plus 131iodine-tositumomab for previously untreated follicular non-Hodgkin lymphoma: SWOG S0016. J Clin Oncol 2013;31:314–20.
[39] Press OW, Unger JM, Braziel RM, et al. Phase II trial of CHOP chemotherapy followed by tositumomab/iodine I-131 tositumomab for previously untreated follicular non-Hodgkin's lymphoma: five-year follow-up of Southwest Oncology Group Protocol S9911. J Clin Oncol 2006;24:4143–9.
[40] Zinzani PL, Tani M, Pulsoni A, et al. Fludarabine and mitoxantrone followed by yttrium-90 ibritumomab tiuxetan in previously untreated patients with follicular non-Hodgkin lymphoma trial: a phase II non-randomised trial (FLUMIZ). Lancet Oncol 2008;9:352–8.
[41] Link BK, Martin P, Kaminski MS, et al. Cyclophosphamide, vincristine, and prednisone followed by tositumomab and iodine-131-tositumomab in patients with untreated low-grade follicular lymphoma: eight-year follow-up of a multicenter phase II study. J Clin Oncol 2010;28:3035–41.
[42] Jacobs SA, Swerdlow SH, Kant J, et al. Phase II trial of short-course CHOP-R followed by 90Y-ibritumomab tiuxetan and extended rituximab in previously untreated follicular lymphoma. Clin Cancer Res 2008;14:7088–94.
[43] Leonard JP, Coleman M, Kostakoglu L, et al. Abbreviated chemotherapy with fludarabine followed by tositumomab and iodine I 131 tositumomab for untreated follicular lymphoma. J Clin Oncol 2005;23:5696–704.
[44] Hainsworth JD, Spigel DR, Markus TM, et al. Rituximab plus short-duration chemotherapy followed by yttrium-90 ibritumomab tiuxetan as first-line treatment for patients with follicular non-Hodgkin lymphoma: a phase II trial of the Sarah Cannon Oncology Research Consortium. Clin Lymphoma Myeloma 2009;9:223–8.
[45] Hornberger J, Reyes C, Lubeck D, et al. Economic evaluation of rituximab plus cyclophosphamide, vincristine and prednisolone for advanced follicular lymphoma. Leuk Lymphoma 2008;49:227–36.
[46] Ray JA, Carr E, Lewis G, et al. An evaluation of the cost-effectiveness of rituximab in combination with chemotherapy for the first-line treatment of follicular non-Hodgkin's lymphoma in the UK. Value Health 2010;13:346–57.
[47] Dewilde S, Woods B, Castaigne J-G, et al. Bendamustine-rituximab: a cost-utility analysis in first-line treatment of indolent non-Hodgkin's lymphoma in England and Wales. J Med Econ 2014;17:111–24.
[48] Blommestein HM, Issa DE, Pompen M, et al. Cost-effectiveness of rituximab as maintenance treatment for relapsed follicular lymphoma: results of a population-based study. Eur J Haematol 2014;92:398–406.
[49] Hagenbeek A. Rituximab maintenance versus radio-immunotherapy consolidation in first remission follicular non-Hodgkin lymphoma. Transfus Apher Sci 2013;49:43.
[50] Guadagnolo BA, Punglia RS, Kuntz KM, et al. Cost-effectiveness analysis of computerized tomography in the routine follow-up of patients after primary treatment for Hodgkin's disease. J Clinical Oncol 2006;24:4116–22.