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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

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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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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.