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BRIEF COMMUNICATION

Rituximab Maintenance for the Treatment of Patients With Follicular Lymphoma: An Updated Systematic Review and Meta-analysis of Randomized Trials

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In a previous systematic review and meta-analysis of five randomized controlled trials comparing rituximab maintenance with no maintenance (observation or rituximab at progression) for patients with follicular lymphoma, we reported that rituximab maintenance treatment improved the overall survival of patients. In this study, we did a similar search of the electronic databases updated through December 31, 2010, and included nine trials and 2586 follicular lymphoma patients. Hazard ratios (HRs) for time-to-event data were estimated and pooled using the inverse variance method. Risk ratios for dichotomous data were pooled using a fixed effect model. Patients treated with rituximab maintenance had improved overall survival (pooled HR of death = 0.76, 95% confidence interval [CI] = 0.62 to 0.92) compared with patients in the no maintenance group. Patients with refractory or relapsed (ie, previously treated) follicular lymphoma treated with rituximab maintenance had improved overall survival (pooled HR of death = 0.72, 95% CI = 0.57 to 0.91), whereas previously untreated patients had no survival benefit (pooled HR of death = 0.86, 95% CI = 0.60 to 1.25). The rate of infection-related adverse events was higher in the rituximab maintenance group (pooled risk ratio = 1.67, 95% CI = 1.40 to 2.00). These results further support the use of rituximab maintenance in the standard of care for refractory or relapsed follicular lymphoma.

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Follicular lymphoma is a "slow growing" B-cell lymphoma. The median age at diagnosis is 63 years (1). Most patients are diagnosed with advanced stage (Ann Arbor stage III or IV) (2) and are followed without chemotherapy until fever, weight loss or night sweats (B symptoms), or signs of high tumor bulk occur, or the lymphoma jeopardizes an organ function (known as the Groupe d'Etude des Lymphomes Folliculaires [GELF] criteria) (3,4). Patients respond well to the initial (first-line) rituximab–chemotherapy induction but typically experience repeated relapses and shortening of the time from treatment to treatment (4). Survival of patients with follicular lymphoma is shorter compared with a matched cohort from the general population, with a median survival of approximately 10 years (95% confidence interval [CI] = 8 to 12 years) (1,5).

Addition of rituximab to induction chemotherapy (rituximab–chemotherapy induction) improves survival of patients with follicular lymphoma compared with induction chemotherapy, but most patients are not cured and experience relapse after a median of 4 years (95% CI = 3.17 to not reached) (6–8). Rituximab maintenance treatment after any induction therapy improves progression-free survival, but evidence of improved overall survival is lacking from randomized controlled trials (9,10). To evaluate the effect of rituximab maintenance treatment on the overall survival of patients with follicular lymphoma, previously we performed a systematic review and meta-analysis (11) of five randomized controlled trials conducted between the years 1998 and 2004 in which 985 follicular lymphoma patients were randomly assigned to rituximab maintenance treatment or to no maintenance (observation or rituximab at progression). Induction therapy consisted of rituximab or chemotherapy or a combination of rituximab and chemotherapy. Results demonstrated a statistically significant survival benefit for patients with refractory or relapsed (ie, previously treated) follicular lymphoma who received rituximab maintenance treatment (pooled hazard ratio [HR] of death = 0.58, 95% CI = 0.42 to 0.79) but not for patients after first-line induction therapy (pooled HR of death = 0.68, 95% CI = 0.37 to 1.25). Since our previous publication (11), the trials included in the systematic review and meta-analysis have published updated results, and in addition, new clinical trials have been completed. In this study, we report an updated systematic review and meta-analysis integrating these new results.

The Cochrane Collaboration policy requires all systematic reviews to be updated within 2 years (12). Because the literature search for this review was done in June 2007, we decided to update it in December 2010. A search for randomized controlled trials was performed as described previously (11). We searched The Cochrane Central Register of Controlled Trials, published in The Cochrane Library (issue 4, 2010); PubMed (1966 to December 2010); EMBASE (1974 to June 2007); LILACS (1982 to December 2010); the database of clinical trials in hematologic malignancies (www.hematology-studies.org); Conference Proceedings of the American Society of Hematology (1995 to 2010), Conference Proceedings of the American Society of Clinical Oncology Annual Meeting (1995 to 2010), and Proceedings of the European Hematology Association; and databases of ongoing and unpublished trials (http://www.controlled-trials.com/, http://www.clinicaltrials.gov/ct, http://clinicaltrials.nci.nih.gov/). The

CONTEXTS AND CAVEATS

Prior knowledge

Most follicular lymphoma patients respond to induction chemotherapy but experience repeated relapses. A previously conducted systematic review and meta-analysis of five randomized controlled trials that compared rituximab maintenance treatment with no maintenance showed survival benefit for patients with refractory or relapsed (previously treated) follicular lymphoma who received rituximab maintenance, but not untreated patients.

Study design

An updated systematic review and meta-analysis was conducted by including nine randomized trials, and patients treated with rituximab maintenance were compared with no maintenance group.

Contribution

Patients treated with rituximab maintenance showed statistically significantly better overall and progression-free survival compared with patients in the no maintenance group. Subgroup analysis of overall survival showed that patients with refractory or relapsed follicular lymphoma had a clear survival benefit with rituximab maintenance treatment, but previously untreated patients did not have a statistically significant survival benefit. A higher rate of infection-related adverse events was noted in the rituximab maintenance group.

Implications

The updated meta-analysis confirms the results of the former meta-analysis. Rituximab maintenance improves survival in previously treated patients, and although untreated patients show progression-free survival benefit, they do not show overall survival benefit. The higher rate of infection-related adverse events in the rituximab maintenance group needs to be considered while treating the patients.

Limitations

An increased chance of false-positive results is possible because of repeated meta-analysis.

From the Editors

terms "follicular" or "indolent" and similar terms, and "lymphoma" and similar terms were cross-searched with "rituximab" or "monoclonal antibodies" and similar terms. We contacted the first or corresponding author of each included trial to obtain complementary information or information on unpublished trials. The primary outcome was overall survival. Secondary outcomes included progression-free survival [as defined in Cheson et al. (13)], quality of life, and adverse events: grade 3 or 4 adverse events ([according to the US National Cancer Institute's Common Terminology Criteria for Adverse Events, CTCAE, version 3]. If the trials used the term grade but did not define the grading system, we assumed grading was defined according to CTCAE), adverse events requiring discontinuation of therapy, infections, and severe infections (as defined in each trial). In our previous protocol designed in 2007, we also planned to analyze event-free survival, rate of disappearance of B-cell CLL/lymphoma 2 (BCL2) protein from biopsy specimen, and response duration. We amended the protocol and did not include these outcome measures in the current meta-analysis.

Subgroup analyses for the primary outcome were planned according to the type of induction therapy (chemotherapy only, rituximab only, rituximab combined with chemotherapy, any regimen containing rituximab), rituximab schedule, treatment line, blinding of patients, caregivers, or outcome assessors, and adequacy of allocation concealment and adequacy of sequence generation. All subgroup analyses of progression-free survival (by type of induction therapy, type of chemotherapy, treatment line) were not planned a priori in the protocol.

Hazard ratios and 95% confidence intervals for time-to-event outcomes were estimated (14,15) and pooled using inverse variance method in a fixed effect model. A hazard ratio less than 1.0 was in favor of rituximab maintenance treatment. Risk ratios (RRs) and 95% confidence intervals for dichotomous data were estimated and pooled using a fixed effect model (the Mantel–Haenszel method) (16). For the primary outcome, we performed a sensitivity analysis by repeating the analysis using a random effects model [the DerSimonian and Laird method; (17)]. We assessed heterogeneity of trial results by the χ^2 test of heterogeneity and the I^2 statistic of inconsistency. Statistically significant heterogeneity was defined as P less than .1 or an I^2 statistic greater than 50% (18). All statistical tests were done by Review Manager (RevMan) version 5.1 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011) and were two-sided.

The literature search identified 873 references, of which 64 references were considered potentially relevant (8–10,19–79), and 50 references were excluded (19–68). Ten trials fulfilled inclusion criteria (8–10,69–79), including five new trials (8,69,73,76–78) and three updated data of trials (71,72,75) included in our previous report (11). One trial did not report relevant clinical data (78). Two of the publications (71,79) reported the outcomes of different subsets of patients from the same trial.

The trial and patient characteristics are shown in Tables 1 and 2. Patients were eligible for trial entry if they had at least partial response (8,10,73–76) or at least stable disease (9,69–72,79) after induction therapy. In one trial (70), patients in the no maintenance group were eligible for rituximab upon progression of follicular lymphoma; in other trials, patients in the control group were observed without rituximab treatment.

Patients included in one trial (69) fulfilled GELF criteria for deferred treatment (3). In the original trial (69), patients were randomly assigned to one of three groups—observation, rituximab induction, or rituximab induction and maintenance. To avoid overestimation of the effect of rituximab maintenance, we chose to compare patients who received rituximab induction and maintenance with those who received rituximab induction only and not with those in the observation group. Thus, in this meta-analysis, patients who received only rituximab induction and no maintenance were used as the control group.

Nine trials performed between 1998 and 2009 (2586 patients) were eligible for the meta-analysis of overall survival (8–10,69–77,79). Patients treated with rituximab maintenance had statistically significantly better overall survival compared with patients in the no maintenance group (pooled HR of death = 0.76, 95% CI = 0.62 to 0.92) (Figure 1). No statistically significant heterogeneity among the trials was observed for overall survival ($P_{\text{heterogeneity}}$ = .0). The funnel plot of the pri-

Table 1. Characteristics of included trials*

Author, year (reference)	No. of randomly assigned patients	No. of patients included in meta-analysis	Quality of allocation concealment†	Quality of sequence generation‡	No. of dropouts (%)	Median follow-up, mo
Ardeshna 2010 (69)	462	276	NR	NR	0 (0)	NR
Forstpointner 2006 (10)	195§	105‖	Adequate	Adequate	19 (10)	26
Hainsworth 2005 (70)	90	90	Adequate	Adequate	0 (0)	41
Hochster 2007 (79); Hochster 2009 (71)	313 (CVP cohort); 69 (FC cohort)¶	228 (CVP cohort)#; 69 (FC cohort)	NR	NR	2 (1)	48
Martinelli 2010 (9,72)	151	151	Adequate	Adequate	0 (0)	114
Pettengell 2010 (73)	280	280	NR	NR	0 (0)	76.8
Salles 2010 (65)	1018	1018	Adequate	Adequate	0 (0)	36
van Oers 2010 (74,75)	334	334	NR	NR	0 (0)	84
Witzens-Harig 2009 (76,77)	171	35§	Adequate	Adequate	8 (5)	28

* CVP = cyclophosphamide, vincristine, prednisone; FC = fludarabine, cyclophosphamide; NR = not reported.

† Adequate allocation concealment secures strict implementation of an allocation sequence without foreknowledge of intervention assignments (as central randomization, opaque, and sealed envelopes).

‡ Adequate sequence (of randomization) is generated by the use of a random component (as random number table, computer random number generator, coin tossing, minimization).

§ Of 195 randomly assigned patients, 19 were lost to follow-up. Of the 176 analyzed patients, 105 had follicular lymphoma.

‖ Separate analysis was possible for patients with follicular lymphoma.

¶ Patients in one trial (71,79) were randomly assigned to CF and CVP and to rituximab maintenance or no maintenance in a second randomization. The CF treatment was closed early. The outcomes of maintenance in these two groups are reported separately for each cohort.

Of the 313 randomly assigned patients, there were 228 available patients with follicular lymphoma.

mary outcome did not support a publication bias (data not shown).

A subgroup analysis of overall survival showed that patients with refractory or relapsed (ie, previously treated) follicular lymphoma (909 patients) (9,10,70,72–75) had a clear survival benefit with rituximab maintenance treatment (pooled HR of death = 0.72, 95% CI = 0.57 to 0.91), whereas previously untreated patients (maintenance after first-line induction therapy) (1650 patients) (8,9,69,71,72,79) did not (pooled HR of death = 0.86, 95% CI = 0.60 to 1.25) (Figure 1, and Supplementary Table 1, available online). Chemotherapy regimen and the schedule of rituximab maintenance had no statistically significant effect on outcome (Supplementary Table 1, available online). Three trials included patients whose induction therapy consisted of single-agent rituximab with no chemotherapy (9,69,70,72). Analysis of these trials (516 patients) showed that rituximab maintenance treatment had no statistically significant effect on overall survival compared with no maintenance therapy (pooled HR of death = 0.76, 95% CI = 0.53 to 1.01). The sensitivity analysis by quality of allocation concealment (adequate or not reported) did not show an effect of quality of concealment on the outcomes (Supplementary Table 1, available online).

In most of the included trials, progression-free survival improved with rituximab maintenance treatment compared with no maintenance (8-10,69–76). The pooled hazard ratios from nine trials (2550 patients) (8,10,69–73,75,76,79) showed a statistically significantly improved progression-free survival (pooled HR of disease progression or death = 0.54, 95% CI = 0.48 to 0.60). This effect was consistent both in previously untreated patients (1650 patients) (8–10,69,71,79) (pooled HR of disease progression or death = 0.52, 95% CI = 0.44 to 0.61) and in those with refractory or relapsed lymphoma (maintenance rituximab after two or more inductions) (909 patients) (9,10,70,72,73,75) (pooled HR of disease progression or death = 0.60, 95% CI = 0.49 to 0.72), following different induction therapies: rituximab alone (516 patients) (9,69,70,72) (pooled HR of disease progression or death = 0.50, 95% CI = 0.39 to 0.65); chemotherapy alone (297 patients) (71,79) (pooled HR of disease progression

Table 2. Characteristics of patients included in the meta-analysis and their treatment*

Author, year (reference)	Grade of lymphoma	Additional inclusion criteria and eligibility for induction	Treatment line	Induction therapy	Minimum response to induction	Rituximab maintenance protocol
Ardeshna, 2010 (69)	1–3A†	Asymptomatic, advanced-stage, low tumor burden (GELF criteria), randomized to observation, or induction, or induction and maintenance	Untreated FL	Rituximab	Stable disease	A single infusion every 2 mo for 2 y
Forstpointner, 2006 (10)	1–3†	No additional	Relapsed (previously treated) FL, MCL‡	FCM or FCM with rituximab	PR	Weekly for 4 wk at 3 and 9 mo
Hainsworth, 2005 (70)	1–2†	Progressive lymphoma, any stage	Relapsed FL, SLL upon progression	Rituximab	Stable disease	Weekly for 4 wk every 6 mo for 2 y
Hochster, 2007 (79); Hochster, 2009 (71)	1–2†	Advanced stage	Untreated FL, SLL‡	CVP, FC	Stable disease	Weekly for 4 wk every 6 mo for 2 y
Martinelli, 2010 (9,72)	1–3 REAL classification§	Any stage (84% advanced)	Untreated and relapsed FL	Rituximab (no previous rituximab)	Stable disease	A single infusion every 2 mo for four doses
Pettengell, 2010 (73)	1–3A†	No additional	Relapsed FL	Standard induction followed by BEAM conditioning and ASCT	PR	A single infusion every 3 mo for 2 y
Salles, 2010 (65)	1–3A†	High tumor burden according (not fulfilling GELF criteria)	Untreated FL	Rituximab with CHOP or CVP or FCM	PR	A single infusion every 2 mo for 2 y
van Oers, 2010 (74,75)	1–3A†	No additional	Relapsed FL	CHOP with rituximab or CHOP	PR	A single infusion every 3 mo for 2 y
Witzens-Harig, 2009 (76,77)	1–3A†	No additional	Untreated and relapsed CD20-positive B-cell non-Hodgkin lymphoma‡	Any	PR	A single infusion every 3 mo for 2 y

* ASCT = autologous stem cell transplantation; BEAM = BCNU, etoposide, cytarabine, melphalan; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; CVP = cyclophosphamide, vincristine, prednisone; FC = fludarabine, cyclophosphamide; FCM = fludarabine, cyclophosphamide, mitoxantrone; FL = follicular lymphoma; GELF = the Groupe d'Etudes Lymphomes Folliculare; MCL = mantle cell lymphoma; mo = months; PR = partial response; SLL = small lymphocytic lymphoma; wk = weeks; y = years.

† Grades according to the World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues.

‡ Separate analysis was possible for patients with follicular lymphoma.

§ Grades according to the Revised European American Lymphoma (REAL) classification.

or death = 0.49, 95% CI = 0.37 to 0.66); and rituximab–chemotherapy (1352 patients) (8,74,75) (pooled HR of disease progression or death = 0.58, 95% CI = 0.48 to 0.70). The benefit in progression-free survival was observed in patients treated with different chemotherapy regimens (with or without rituximab); in patients treated with cyclophosphamide, vincristine, adriamycin, and prednisone, the pooled hazard ratio for disease progression or death was 0.53 (95% CI = 0.44 to 0.64), with cyclophosphamide, vincristine, and prednisone the pooled hazard ratio of disease progression or death was 0.50 (95% CI = 0.38 to 0.66), with fludarabine-containing regimen the hazard ratio of disease progression or death was 0.58 (95% CI = 0.40 to 0.84).

In two trials, the quality of life was assessed and censored at the time of progression (8,77). As shown in each of these trials, rituximab maintenance did not impair the quality of life. We could not analyze quality of life in the meta-analysis because of the scarcity of data.

Rituximab maintenance treatment was associated with a higher rate of grade 3 or 4 adverse events compared with the no maintenance (1598 patients) (8–10,69) (RR = 1.60, 95% CI = 1.29 to 1.99). Rituximab maintenance group was also associated with a higher rate of infections compared with no maintenance (1656 patients) (8–10,74,75) (pooled RR = 1.67, 95% CI = 1.40 to 2.00). When only grade 3 or 4 infection–related adverse events were included in the analysis (1656 patients) (8,10,72,74,75), rituximab maintenance was associated with an even higher rate compared with no maintenance (pooled RR = 3.55, 95% CI = 1.88 to 6.69). A higher rate of adverse events requiring discontinuation of rituximab (1433 patients) (8,70,74) was associated with rituximab maintenance group compared with no maintenance group (pooled RR = 2.72, 95% CI = 1.30 to 5.68).

Rituximab maintenance improved overall survival and disease control in patients with follicular lymphoma who responded to induction therapy (P = .006). The accumulating data from new and updated clinical trials strengthen the results of our former meta-analysis (11). The large sample size and longer follow-up period in some of the trials consolidate the results of

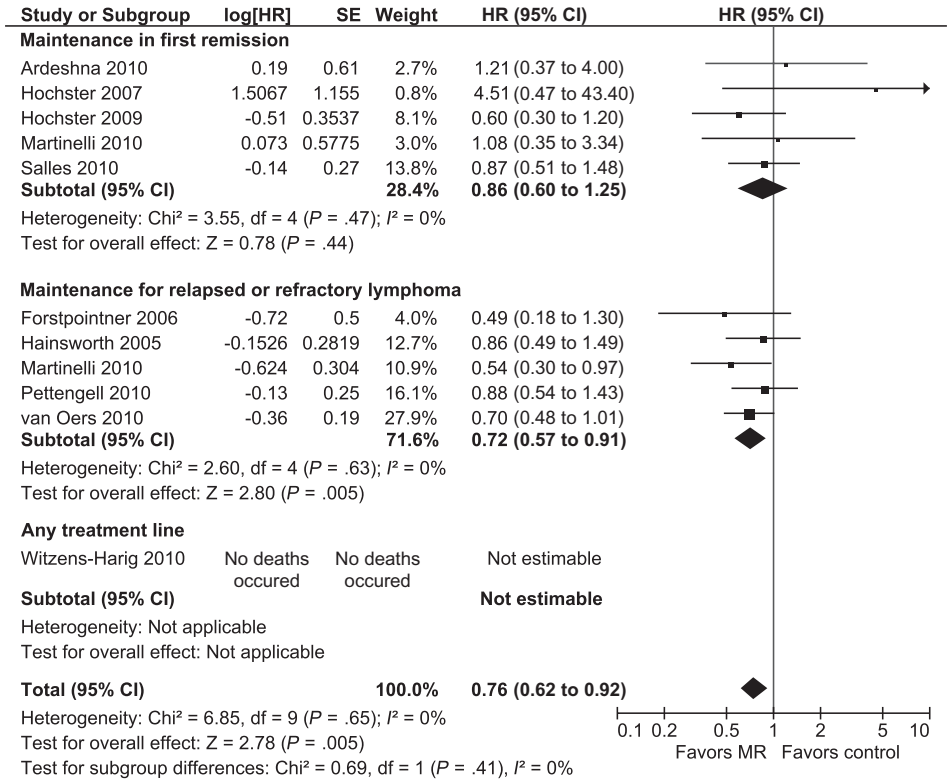

Figure 1. Pooled hazard ratios (HRs) of overall survival of patients with follicular lymphoma after first induction and refractory or relapsed disease. Nine trials were included in meta-analysis; no death occurred in one trial (76), and it did not contribute to the pooled analysis. **Black squares** represent the point estimate (HR), their **sizes** represent their weight in the pooled analysis, and the **horizontal bars** represent the 95% confidence intervals (CIs), **unidirectional arrows** represent a limit of the CI that is higher than 10, and the **center of the black diamonds** represent the pooled point estimate, and their **horizontal axis** represents the pooled 95% CI. The **black diamond** at the bottom represents the pooled point estimate. MR = maintenance therapy with rituximab. SE = standard error.

this study. Although a clear survival benefit of rituximab maintenance was observed only for patients with relapsed or refractory follicular lymphoma, the magnitude of progression-free survival benefit was similar after first induction as well as after two or more inductions, and was consistent in different subgroups of patients.

A limitation of repeating the meta-analysis is the increased chance of false-positive results. The reported point estimates and confidence intervals were not adjusted for repeated analyses.

The highly statistically significant progression-free survival benefit of rituximab maintenance was not translated to a statistically significant overall survival benefit after first induction treatment in patients with follicular lymphoma. This may be because a longer follow-up is required to demonstrate a statistically significant difference in survival of patients in first remission whose estimated survival is in the range of decades (1,80), as opposed to few years in patients in second or third remission. Alternatively, disease progression per se may not always be a clinically meaningful event, and second-line treatment may be efficient in these patients. Thus, for patients with relapsed follicular lymphoma who responded to induction therapy, rituximab maintenance should be considered the standard of care. For first-line, treatment options should be discussed with patients in light of the statistically significant prolongation of progression-free survival vs increased rate of infections.

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