Immunochemotherapy With Rituximab and Overall Survival in Patients With Indolent or Mantle Cell Lymphoma: A Systematic Review and Meta-analysis

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Background Addition of the anti-CD20 monoclonal antibody rituximab to chemotherapy (R-chemo) has been shown to improve response rates and progression-free survival in patients with indolent or mantle cell lymphoma. However, the impact of R-chemo on overall survival is unclear. We performed a comprehensive systematic review and meta-analysis to examine the efficacy of combined immunochemotherapy using R-chemo compared with the identical chemotherapy alone with respect to overall survival in patients with advanced indolent lymphoma or mantle cell lymphoma.

Methods Medical databases and conference proceedings were searched for randomized controlled trials published from January 1990 through December 2005 that compared R-chemo with chemotherapy alone in patients with newly diagnosed or relapsed indolent lymphoma or mantle cell lymphoma. We included full-text and abstract publications. Endpoints were overall survival, disease control, overall response, and toxicity. A fixed-effects model was assumed in all meta-analyses. For binary data, the relative risk was used as an indicator of treatment effect, and the Mantel–Haenszel method was used to pool relative risks. Statistical tests for heterogeneity were one-sided; statistical tests for effect estimates were two-sided.

Results Seven randomized controlled trials involving 1943 patients with follicular lymphoma, mantle cell lymphoma, or other indolent lymphomas were included in the meta-analysis. Five studies were published as full-text articles, and two were in abstract form. Patients treated with R-chemo had better overall survival (hazard ratio [HR] for mortality = 0.65; 95% confidence interval [CI] = 0.54 to 0.78), overall response (relative risk of tumor response = 1.21; 95% CI = 1.16 to 1.27), and disease control (HR of disease event = 0.62; 95% CI = 0.55 to 0.71) than patients treated with chemotherapy alone. R-chemo improved overall survival in patients with follicular lymphoma (HR for mortality = 0.63; 95% CI = 0.51 to 0.79) and in patients with mantle cell lymphoma (HR for mortality = 0.60; 95% CI = 0.37 to 0.98). However, in the latter case, there was heterogeneity among the trials ($P = .07$), making the survival benefit less reliable.

Conclusion In patients with indolent or mantle cell lymphoma, R-chemo is superior to chemotherapy alone with respect to overall survival.

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Non-Hodgkin lymphoma, one of the leading causes of cancer death in the United States and Europe, has been classified into two types: aggressive (i.e., fast growing) and indolent (i.e., slow growing) (1). Patients with aggressive B-cell lymphoma are potentially curable when treated with multiagent chemotherapy such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) (2). The standard of care for patients with aggressive lymphoma has changed recently with the implementation of therapy with the chimeric anti-CD20 monoclonal antibody rituximab (3). Combination treatment with rituximab and CHOP (R-CHOP) or similar regimens has resulted in superior treatment outcomes compared with multiagent chemotherapy alone, making combined immunochemotherapy with rituximab (R-chemo) the new standard of care for this group of patients (4,5).

The clinical course of indolent lymphoma, which make up 70% of non-Hodgkin lymphoma, and the therapeutic approach differs

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from that of aggressive lymphoma. Prognosis and therapy for indolent lymphoma are closely related to the extent of the disease at initial diagnosis: less than 15%–20% of patients with indolent lymphoma are diagnosed at an early stage of the disease (Ann Arbor stage I or II), and half of these patients experience long-term disease-free survival after radiotherapy (6). However, the vast majority of patients with indolent lymphoma are diagnosed with advanced-stage disease (i.e., Ann Arbor stage III or IV) and cannot be cured with conventional therapy. These patients do not have a survival benefit from early treatment at diagnosis as compared with a watch-and-wait strategy, and it is generally accepted that treatment for such patients should be deferred until the disease becomes symptomatic (7–9). For patients with symptomatic indolent lymphoma, many therapeutic options are available, ranging from single agents to multiagent regimens or high-dose chemotherapy (10–12).

The course of treatment for patients with symptomatic indolent lymphoma is typically characterized by a high initial response rate followed by relapse, and there are no, or very few, long-term survivors. Therefore, the prognosis for patients with indolent lymphoma, for whom the median survival is 8–10 years, has changed very little over the last decades (13). More recent survival data for patients with advanced indolent lymphoma suggest that overall survival has improved over the last 25 years, probably because of sequential application of different chemotherapy regimens, the use of biologic agents, and improved supportive care (14,15).

Approximately 3%–10% of all non-Hodgkin lymphomas are mantle cell lymphomas, which are often classified as an indolent lymphoma variant because some patients with this disorder survive for many years without treatment. However, many patients with mantle cell lymphoma have more aggressive disease, and for them, the median overall survival is 3–5 years. Therefore, it is now recommended (16) that therapy for mantle cell lymphoma be initiated at the time of diagnosis. Indeed, most investigators currently consider mantle cell lymphoma to be an aggressive lymphoma, whereas in the past, patients with mantle cell lymphoma were mostly included in clinical trials of indolent lymphoma.

R-CHOP has shown impressive response rates and prolonged progression-free survival in patients with indolent and mantle cell lymphomas (17,18). Randomized phase III trials in which rituximab was added to a variety of different regimens confirmed these benefits in previously treated as well as in untreated patients with advanced indolent lymphoma (18–21,32). Some of these trials (20,21,32) have suggested a trend toward improved overall survival for patients treated with R-chemo, but the benefit was not definitive.

We conducted a systematic review and meta-analysis of randomized controlled trials in which patients with advanced indolent lymphoma and mantle cell lymphoma were randomly assigned to receive R-chemo or chemotherapy alone. The aim of this study was to examine the efficacy of combined immunochemotherapy using R-chemo compared with identical chemotherapy alone with respect to overall survival. Other endpoints included response rate, toxicity, and disease control as assessed by measures such as time to treatment failure, event-free survival, progression-free survival, and time to progression. The impact of maintenance therapy and sequential therapy with rituximab or other immunoconjugates was not addressed.

CONTEXT AND CAVEATS

Prior knowledge

Although the addition of the anti-CD20 monoclonal antibody rituximab to chemotherapy (R-chemo) has been shown to improve response rates and progression-free survival in patients with indolent or mantle cell lymphoma, the efficacy of R-chemo with respect to overall survival is unclear.

Study design

Meta-analysis of randomized controlled trials.

Contribution

Patients treated with R-chemo had better overall survival, overall response, complete response, and disease control but more leukocytopenia and fever than patients treated with chemotherapy alone. R-chemo improved overall survival in patients with follicular lymphoma.

Implications

Concomitant treatment with rituximab and standard chemotherapy regimens should be considered the standard of care for patients with indolent and mantle cell lymphomas who require therapy and for patients with follicular lymphoma.

Limitations

Variability in treatment regimens among trials precluded determination of which chemotherapy regimen is the best to combine with rituximab or about the optimal number of cycles needed to treat patients with indolent lymphoma. Heterogeneity among the analyzed mantle cell lymphoma trials precluded reliable assessment of efficacy of R-chemo with respect to overall survival.

Methods

Literature Search

To ensure retrieval of all relevant trials, we used a broad search strategy in which key words and text words related to lymphoma and rituximab were combined with a validated methodologic filter, as described by Dickersin et al. (22). We used this strategy to search a variety of electronic databases, including the Cochrane Controlled Trials Register, Medline, EMBASE, LILaC, and Internet databases of ongoing clinical trials. The electronic databases were initially searched in April 2002 (period covered: from January 1990 through March 2002), and the search was updated in December 2005 (period covered: April 2002 through December 2005). We also manually searched the conference proceedings of the American Society of Hematology (ASH), the American Society of Clinical Oncology (ASCO), and the European Society of Medical Oncology for relevant clinical trials.

Investigators and pharmaceutical companies identified as being active in the field were asked to provide unpublished data or studies. We also contacted hemato-oncologic study groups, including the Eastern Cooperative Oncology Group, the Southwestern Oncology Group, the National Cancer Institute, the European Organisation for Research and Treatment of Cancer (EORTC), ASH, and ASCO. No language restrictions

were used. The full search strategy is published in the Cochrane Library (23).

Inclusion Criteria

We included in this analysis only randomized controlled trials that enrolled patients who were older than 18 years and who had histologically proven indolent lymphoma or mantle cell lymphoma, regardless of stage of disease or previous therapy received, and that compared R-chemo with the same chemotherapy alone. We included data from full-text articles and abstracts and unpublished data. We excluded ongoing studies, interim analyses, nonrandomized studies, and studies with 10 or fewer patients per study arm. Studies on patients with human immunodeficiency virus or primary central nervous system lymphoma were excluded.

Study Selection, Quality Assessment, and Data Extraction

Two reviewers (H. Schulz and N. Skoetz) independently screened the titles and abstracts of all studies identified in the literature search to verify compliance with the inclusion and exclusion criteria. When this information was unsatisfactory, we performed a full-text analysis that considered the defined inclusion and exclusion criteria. Disagreements between the two reviewers were resolved by consensus involving a third reviewer (A. Engert). The same reviewers who screened the studies independently performed data extraction and quality assessment of all included articles.

Assessment of the methodologic quality of clinical trials requires information about the design, conduct, and analysis of the trial (24). All included studies, regardless of whether they are published or not, were assessed for internal validity parameters, with particular emphasis on randomization, masking of patients and clinicians, concealment of allocation, documentation of dropouts and withdrawals, and intent-to-treat analysis. We contacted the first authors of the included studies to obtain unreported data.

Data Analysis and Statistical Methods

A fixed-effects model was assumed in all meta-analyses. For binary data, the relative risk (RR) was used as an indicator of treatment effect, and the Mantel–Haenszel method was used to pool relative risks. Endpoints were overall survival, disease control, overall response, and toxicity. Response was defined according to the International Working Group Criteria (25) and side effects according to the National Cancer Institute of Canada Common Toxicity Criteria. Overall survival and disease control were calculated as hazard ratios (HRs) with data from published studies using methods described in Parmar et al. (26). The number of patients needed to treat for overall survival was calculated by assuming a 2-year overall survival of 90% for patients with follicular lymphoma (15), as described by Altman and Andersen (27). In meta-analyses with at least four trials, a funnel plot was generated, and a linear regression test (28) was performed to examine whether there was publication bias. A P value less than .1 was considered to be statistically significant for the linear regression test.

Potential causes of heterogeneity were explored by performing sensitivity analyses to evaluate effects of lymphoma subtype, previous treatment, stage, study duration, study quality, the source of the data, and the influence of single large studies on the effectiveness of rituximab treatment. Particular emphasis was placed on the evaluation of additional side effects of R-chemo in comparison to chemotherapy alone. Side effects were defined as any adverse event occurring during treatment, including death (according to World Health Organization grading).

Analyses were performed using the computer program Review Manager (RevMan; version 4.2 for Windows. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2003). The statistical software package R (29) was used for additional analyses that were not possible with RevMan. Statistical tests for heterogeneity were one-sided; statistical tests for effect estimates and publication bias were two-sided.

Results

Identification of Studies

Overall, 1345 potentially relevant references and citations describing treatment related to lymphoma and rituximab were identified and screened for retrieval. Of these, 1283 were excluded because they did not meet inclusion criteria; the remaining 62 articles were selected for full-text analysis and were evaluated in more detail. Of these, 55 were excluded for the following reasons: 33 articles were reviews; two articles described ongoing trials; two trials did not use identical chemotherapy in the control arm; five trials were not randomized; 11 studies proved rituximab as monotherapy, maintenance therapy, consolidation therapy, in combination with radiotherapy, or as sequential treatment. These studies were excluded because they did not compare concurrent R-chemo as an induction therapy with an identical chemotherapy alone. Two trials evaluated minimal residual disease but not overall survival or disease control. The remaining seven randomized controlled trials (Table 1), which involved 1943 adult patients, met all the inclusion and exclusion criteria and were included in the systematic review and meta-analysis. Among the patients in these trials, 1480 had histologically proven follicular lymphoma and 260 had mantle cell lymphoma. The remaining 203 patients were described as having indolent lymphoma (n = 121) or lymphoplasmocytic/cytoid lymphoma or B-cell chronic lymphocytic leukemia (n = 82) (Table 1).

Five trials (18,19,21,31,32) included untreated patients with advanced disease [i.e., Ann Arbor stage III or IV (33)]. The other two trials (20,30) included relapsed or refractory patients with follicular or mantle cell histology. The chemotherapy regimens used included CHOP; cyclophosphamide, mitoxantrone, vincristine, and prednisone (CNOP); cyclophosphamide, vincristine, and prednisone (CVP); fludarabine, cyclophosphamide, and mitoxantrone (FCM); and mitoxantrone, chlorambucile, and prednisolone (MCP). All trials compared one of these regimens in combination with rituximab (indicated as R-chemo) with the chemotherapy regimen alone (Table 1). In one trial (31), patients were also randomly assigned to a third group to assess treatment with rituximab alone; those patients were not included in this meta-analysis. In two trials of R-CHOP versus CHOP, patients who were younger than 60 years (21) or younger than 65 years (18) and in remission were eligible for a second random assignment to adjuvant treatment with high-dose chemotherapy followed by either blood stem cell transplantation or interferon alpha maintenance; patients in remission who were 60 years or older (21) or 65 years or older (18) received interferon alpha maintenance. Two studies, one of the

Table 1. Summary of trials included in the meta-analysis*

First author, year (reference)	No. of patients				Study arms	Previous therapy	Stage‡	Observation time (mo)	Intent-to-treat analysis	Allocation concealed	Dropouts (%)	Source of data
	Total	Follicular lymphoma	Mantle cell lymphoma	Other†								
Lenz, 2005 (18)	122	0	122	0	R-CHOP/ CHOP	No	III/IV	18	Yes	Yes	5	Full text
Rivas-Vera, 2005 (31)	121	NA	NA	121	R-CNOP/ CNOP/R	No	III/IV	24	No	NA	6	Abstract
Marcus, 2005 (19)	321	321	0	0	R-CVP/ CVP	No	III/IV	18	Yes	Yes	1	Full text
Forstpointner, 2004 (20)	128	65	48	15	R-FCM/ FCM	Yes	III/IV	18	Yes	Yes	13	Full text
Herold, 2004 (32)	358	201	90	67	R-MCP/ MCP	No	III/IV	36	Yes	Yes	0	Abstract
Hiddemann, 2005 (21)	428	428	0	0	R-CHOP/ CHOP	No	III/IV	36	Yes	Yes	0	Full text
van Oers, 2006 (30)	465	465	0	0	R-CHOP/ CHOP	Yes	III/IV	39	Yes	Yes	0	Full text

* R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; NA = not applicable; R-CNOP = rituximab, cyclophosphamide, mitoxantrone, vincristine, and prednisone; R-CVP = rituximab, cyclophosphamide, vincristine, and prednisone; R-FCM = rituximab, fludarabine, cyclophosphamide, and mitoxantrone; R-MCP = rituximab, mitoxantrone, chlorambucile, and prednisolone.

† Not specified indolent lymphoma.

‡ Ann Arbor classification (33).

FCM regimen combined with rituximab versus FCM (20) and the other of R-CHOP versus CHOP (30) offered patients in remission a second random assignment to either rituximab maintenance or observation. All the trials that offered a second random assignment showed a balanced distribution of the baseline characteristics of the patients included in the initial R-chemo and chemotherapy arms.

Study Quality

Quality assessment of the included trials is shown in Table 1. All studies were described by the authors as randomized, and in six of seven trials, the method for concealing allocation was judged to be adequate. The method of allocation concealment was not described in the trial of Rivas-Vera et al. (31). Most of the studies included intent-to-treat calculations, and few dropouts were described. Five studies (18–21,30) were published as full-text articles, and two (31,32) were published in abstract form. For two (20,32) of the seven trials, additional unpublished data were provided by the investigators.

Toxicity

We observed a lack of uniformity related to the reporting of treatment-associated side effects described between the seven selected trials. Three trials (18,20,21) analyzed toxicity over treatment cycles rather than recording absolute numbers of adverse events. Therefore, we could not include these three trials in the meta-analysis of side effects. We performed a meta-analysis of adverse events among the four trials that reported absolute numbers of adverse events (19,30–32). Overall, toxicity was described as mild to moderate for both treatment groups. The most often reported grade 3 and 4 adverse events were hematotoxicity (i.e., leukocytopenia, thrombocytopenia, or granulocytopenia), fever, and infection. The relative risk for developing fever or leukocytopenia was statistically significantly higher in patients treated with R-chemo than in patients treated with chemotherapy alone (RR = 3.79; 95% confidence interval [CI] = 1.47 to 9.78 and RR = 1.31; 95% CI = 1.11 to 1.55, respectively). There was no difference between treatment groups with respect to the risk of infection (Table 2).

Overall Response

The data for 1914 available patients were analyzed for overall response. Among all patients with either indolent lymphoma or mantle cell lymphoma, 854 of 979 patients in the R-chemo group responded to treatment, compared with 673 of 935 patients in the chemotherapy-alone group, corresponding to a relative risk of a response for R-chemo versus chemotherapy of 1.21 (95% CI = 1.16 to 1.27) (Fig. 1, A). The rate of complete responses was statistically significantly higher in patients treated with R-chemo than in patients treated with chemotherapy alone (RR = 2.03; 95% CI = 1.71 to 2.40) (Fig. 1, B). In both analyses, there was

Table 2. Most frequent side effects*

Side effect	No. of trials (references)	R-chemo†	Chemotherapy†	RR (95% CI)
Leukocytopenia	2 (19,32)	149/345	110/336	1.31 (1.11 to 1.55)
Fever	2 (30,32)	21/249	5/232	3.79 (1.47 to 9.78)
Infection	4 (19,30–32)	61/645	56/622	1.05 (0.74 to 1.48)
Thrombocytopenia	4 (19,30–32)	45/645	38/622	1.14 (0.76 to 1.72)
Granulocytopenia	3 (19,30,31)	180/462	149/445	1.18 (1.00 to 1.38)

* Side effects of grade 3 or 4, according to the National Cancer Institute of Canada Common Toxicity Criteria. R-chemo = rituximab in combination with chemotherapy; RR = risk ratio; CI = confidence interval.

† Number of events/number of patients.

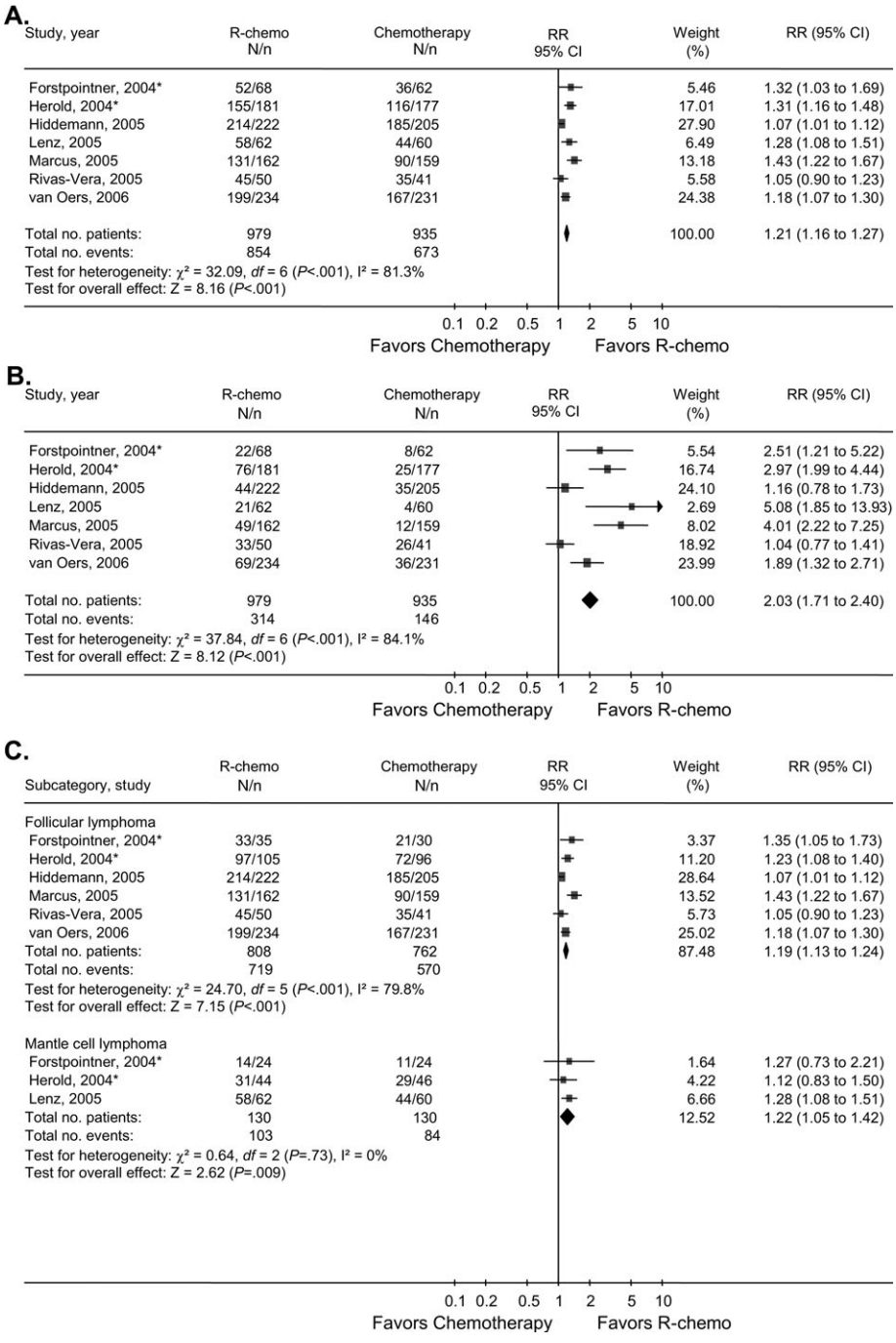

Fig. 1. Meta-analysis of the relative risk (RR) for overall response and complete response for patients receiving rituximab with chemotherapy (R-chemo) or chemotherapy alone. **A**) Overall response for all patients with indolent or mantle cell lymphoma. **B**) Complete response for all patients with indolent or mantle cell lymphoma. **C**) Overall response for the subgroups of patients with follicular lymphoma or mantle cell lymphoma. N = number of events; n = number of patients. **Solid squares** represent risk estimates for the single studies. The size of the **squares** represents the weight assigned to the individual study in the meta-analysis and is proportional to the inverse variance of the estimate. **Horizontal lines** indicate 95% confidence intervals (CIs). Wide confidence intervals are truncated with an **arrow**. The **diamond** shows the 95% confidence intervals for the pooled relative risks. Values greater than 1.0 indicate relative risks that favor R-chemo. *Includes unpublished data provided by the investigators in October 2005.

statistically significant heterogeneity among the trials (*P*<.001). Subgroup analyses of follicular lymphoma patients and mantle cell lymphoma patients also revealed that the R-chemo arms had statistically significant higher overall response (Fig. 1, C) and complete response (data not shown) rates than the chemotherapy-only arms.

Disease Control

The seven trials included in the meta-analysis described different endpoints for treatment outcome, including event-free survival, time to treatment failure, progression-free survival, and time to progression. Documentation of resistance to initial therapy or death was available for 1913 patients. With respect to disease control, R-chemo was statistically significantly superior to chemotherapy alone, with a pooled HR of 0.62 (95% CI = 0.55 to 0.71) (Fig. 2). This advantage was also seen in subgroup analyses comparing different defined intervals between the start of treatment and the documentation of death or progressive disease or between the end of treatment and the documentation of progressive disease or death (data not shown). R-chemo was also statistically significantly superior to chemotherapy alone when subgroups of follicular lymphoma and mantle cell lymphoma were analyzed (data not shown).

Overall Survival

Overall survival data were available for all 1943 patients included in the seven trials. The median observation time for all patients was

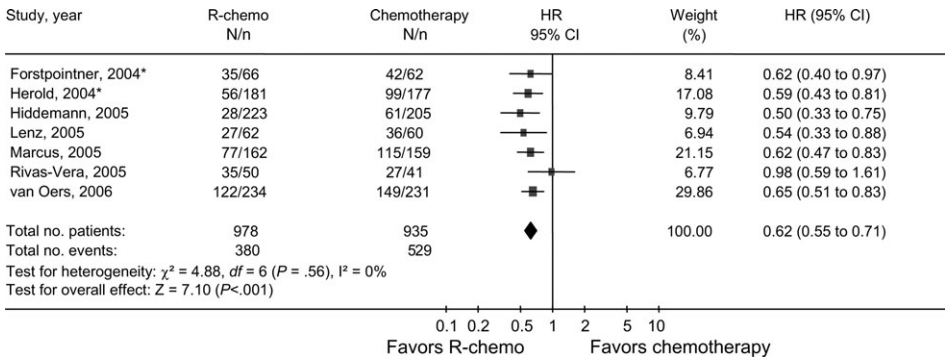

Fig. 2. Meta-analysis of disease control for all patients with indolent or mantle cell lymphoma receiving rituximab with chemotherapy (R-chemo) or chemotherapy alone. Disease control is shown as the hazard ratio (HR) for a disease event (progression, relapse, death). N = number of events; n = number of patients. **Solid squares** represent risk estimates for the single studies. The size of the **squares** represents the weight assigned to the individual study in the meta-analysis and is proportional to the inverse variance of the estimate. **Horizontal lines** indicate 95% confidence intervals (CIs). The **diamond** shows the 95% confidence intervals for the pooled hazard ratios. Values less than 1.0 indicate hazard ratios that favor R-chemo. *Includes unpublished data provided by the investigators in October 2005.

24 months (range = 18–39 months). There was no heterogeneity among trials ($P = .62$). On the basis of results reported by the individual studies, we calculated a pooled hazard ratio for death from any cause of 0.65 (95% CI = 0.54 to 0.78), indicating statistically significantly better overall survival in the R-chemo group compared with the chemotherapy-alone group (Fig. 3, A). A sensitivity analysis revealed no differences between the studies with respect to whether the patients received previous treatment, the quality of the study, or whether the data were from published versus unpublished sources (data not shown).

A total of 1480 patients from five studies were included in our subgroup analysis of overall survival in follicular lymphoma. Of these patients, 759 were treated with R-chemo, of whom 97 died, and 721 were treated with chemotherapy alone, of whom 142 died. There was no heterogeneity among the trials ($P = .59$). The pooled hazard ratio for mortality for patients with follicular lymphoma was 0.63 (95% CI = 0.51 to 0.79), which indicates statistically significantly better overall survival in the R-chemo group than in chemotherapy-alone group (Fig. 3, B). Assuming a 2-year overall survival rate of 90% for patients with follicular lymphoma and the

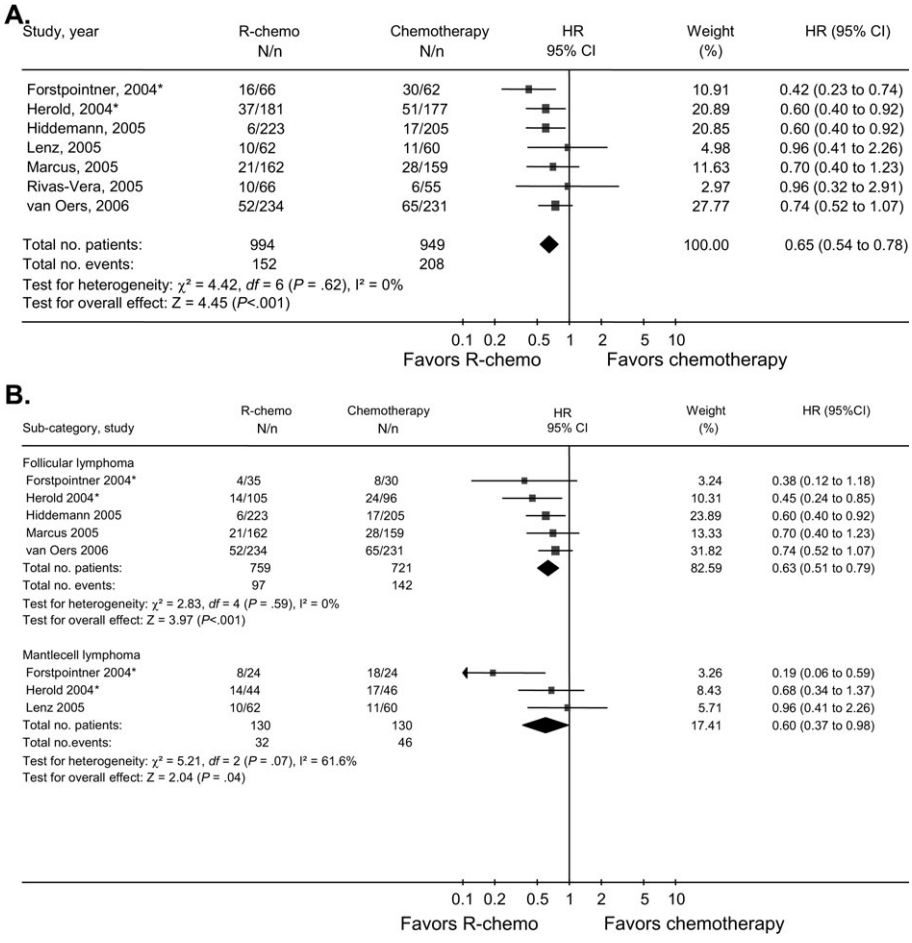

Fig. 3. Meta-analysis of overall survival among patients who received rituximab with chemotherapy (R-chemo) or chemotherapy alone. Overall survival is shown as the hazard ratio (HR) for death from any cause. **A**) Overall survival for all patients with indolent or mantle cell lymphoma. **B**) Overall survival for the subgroups of patients with follicular lymphoma or mantle cell lymphoma. N = number of events; n = number of patients. **Solid squares** represent risk estimates for the single studies. The size of the **squares** represents the weight assigned to the individual study in the meta-analysis and is proportional to the inverse variance of the estimate. **Horizontal lines** indicate 95% confidence intervals (CIs). Wide confidence intervals were truncated with an **arrow**. The **diamonds** show the 95% confidence intervals for the pooled hazard ratios. Values less than 1.0 indicate hazard ratios that favor R-chemo. *Includes unpublished data provided by the investigators in October 2005.

estimated hazard ratio of 0.63, the number of patients who would need to be treated with R-chemo to prevent one additional death in 2 years was 28 (95% CI = 21 to 49.7).

For the subgroup analysis of patients with mantle cell lymphoma, we included three trials with a total of 260 patients. The calculated hazard ratio for death was 0.60 (95% CI = 0.37 to 0.98), which also indicated an advantage for the R-chemo group (Fig. 3, B). However, there was heterogeneity among the trials (P = .07). In a sensitivity analysis that excluded the study by Forstpointner et al. (20), which included patients who had relapsed and who had refractory disease, the heterogeneity disappeared (P = .54), but there was still an overall survival advantage for R-chemo compared with chemotherapy alone, with a pooled hazard ratio for mortality of 0.78 (95% CI = 0.45 to 1.35).

Discussion

Four major results emerged from this systematic review and meta-analysis comparing R-chemo with chemotherapy alone in a total of 1943 patients with follicular lymphoma (n = 1480), mantle cell lymphoma (n = 260), and other indolent lymphomas (n = 203). First, concurrent treatment with R-chemo improved overall survival in these patients compared with chemotherapy alone. Second, patients treated with R-chemo had statistically significantly better overall response, complete response, and disease control than patients treated with chemotherapy alone. Third, subgroup analyses revealed statistically significant and robust data for improved overall response, complete response, disease control, and overall survival in patients with follicular lymphoma; the data were less convincing for mantle cell lymphoma because of heterogeneity among the trials. Fourth, patients treated with R-chemo had statistically significantly more leukocytopenia and fever than patients treated with chemotherapy alone, but there were no differences in the frequencies of infections or thrombocytopenia between the groups.

To our knowledge, this comprehensive evaluation is the first meta-analysis to demonstrate that R-chemo improves overall survival in patients with advanced-stage indolent and mantle cell lymphomas compared with chemotherapy alone. There are two possible explanations for the survival advantage of R-chemo: patients treated with R-chemo may have higher initial response rates and/or prolonged disease control compared with patients treated with chemotherapy alone. The efficiacy of rituximab as single-agent therapy was originally demonstrated in a pivotal study (34) that included 166 patients with refractory or relapsed indolent B-cell non-Hodgkin lymphoma; the overall response rate was 48%. Early preclinical data suggested that rituximab potentiates the sensitivity of tumor cells to cytoxic drugs (35).

The antilymphoma activity of R-chemo reflects their different modes of action and the ability of the antibody to modify molecular signaling pathways. This latter effect is associated with decreased expression of the antiapoptotic gene products, Bcl-2 and Bcl-xL, and the sensitization of drug-resistant B-cell non-Hodgkin lymphoma cells to chemotherapy (36–38). However, the contribution of these mechanisms to the cytoxicity of rituximab and the in vivo relevance of these pathways in patients with follicular or mantle cell lymphoma is unclear. One of the first multicenter phase II trials to use R-CHOP in patients with indolent lymphoma reported an overall response rate of 95% of all assessable patients and a complete response rate of 55% (39). A recent update (17) of this trial reported a median time to progression of 82.3 months and a duration of response of 83.5 months. In this trial, of eight patients who were Bcl-2 positive at baseline, seven became Bcl-2 negative, and three of the seven remained Bcl-2 negative and in ongoing remission at 85, 98, and 99 months.

To date, the most comprehensive summary of prospective clinical trials evaluating R-chemo has been provided by the Hematology Disease Site Group (40). Their systematic review, which included seven randomized controlled trials, suggested that R-chemo should be used in previously untreated and treated patients with follicular or other indolent B-cell non-Hodgkin lymphomas. This recommendation was based on the balance between the risks of toxicity associated with rituximab and the benefits of delaying recurrent disease and the toxicity associated with re-treatment. However, the trials included in that systematic review did not show statistically significant improved overall survival for patients with follicular and other indolent lymphomas, and a meta-analysis was not performed.

Our study has several limitations. First, the studies included in this analysis offered a variety of chemotherapy regimens, such as CHOP, CNOP, FCM, CVP, and MCP. The number of cycles scheduled applied ranged from four to eight, depending on the application of additional consolidation treatment. Options ranged from no adjuvant treatment to high-dose chemotherapy and stem cell transplantation. Therefore, with the currently available data, we cannot comment about which chemotherapy regimen is the best to combine with rituximab or about the optimal number of cycles needed to treat patients with indolent lymphoma.

Second, although two trials (19,21) included in this analysis showed that the addition of rituximab to chemotherapy reduced the risk of disease progression in both low- and high-risk patients, the data were insufficient to perform subgroup analyses on the basis of prognostic scores and biologic parameters (41,42).

Third, only three randomized controlled studies (18,20,32) included patients with mantle cell lymphoma. Although we found that mantle cell lymphoma patients who were treated with R-chemo had better overall survival, disease control, and overall response than patients treated with chemotherapy alone, the evidence for improved overall survival was less reliable than that for patients with follicular lymphoma because of the statistically significant heterogeneity among the analyzed mantle cell lymphoma trials. This heterogeneity was caused mainly by the study of Forstpointner et al. (20), which included relapsed or refractory patients with mantle cell lymphoma, whereas the two other studies enrolled untreated patients only.

There is a clear need for more prospective randomized trials in patients with advanced indolent lymphoma, with separated and adequately powered trials for untreated patients and patients with relapsed or refractory mantle cell lymphoma. These trials should focus on the impact of rituximab in different risk groups and on the intensity of chemotherapy needed for favorable low-risk patients, as is the ongoing Primary Rituximab and Maintenance study (43),

which is evaluating the role of maintenance rituximab in first-line therapy.

The impact of maintenance treatment with rituximab on overall survival, which was not evaluated in this analysis, is one of the most important open questions for patients with indolent non-Hodgkin lymphoma. Recent randomized trials performed by the German Low Grade Lymphoma Study Group (GLSG) and by the EORTC demonstrated the superiority of rituximab maintenance after immunochemotherapy (30,44) and after chemotherapy (30) compared with observation alone. However, the present review analyzed trials conducted at a time of the rituximab era, when rituximab use was restricted to patients with relapsed disease. Therefore, the difference in overall survival between patients treated initially with immunochemotherapy or chemotherapy alone followed by maintenance therapy with rituximab might be smaller in current and future practice. There is also a need for additional randomized controlled trials in patients with mantle cell lymphoma to test the addition of rituximab to more intense chemotherapy regimens, such as dexamethasone, high-dose cytarabine, and cisplatin or hyperfractionated cyclophosphamide, doxorubicin, vincristine, and dexamethasone followed by stem cell transplantation, or rituximab in combination with other new treatment drugs.

In conclusion, this meta-analysis demonstrated that, in patients with indolent or mantle cell lymphoma, R-chemo is superior to chemotherapy alone with respect to remission induction, progression-free survival, and overall survival. Therefore, concomitant treatment with rituximab and standard chemotherapy regimens should be considered the standard of care for patients with indolent and mantle cell lymphomas who require therapy and for patients with follicular lymphoma.

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Notes

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