Follicular lymphoma (FL) is the most common indolent non-Hodgkin lymphoma (1,2) and generally has a long natural history with multiple remissions and relapses (3). Randomized control trials (RCTs) of multiple chemotherapy regimens have resulted in varying event-free survival (EFS) but have not indicated a survival advantage attributed to one regimen compared with another (4–6). The addition of interferon alpha to chemotherapy improves overall survival (OS) but is associated with substantial toxicity and is not generally accepted as standard therapy (7). Several RCTs of patients with FL have demonstrated the benefit of adding rituximab to primary therapy (8) with regard to OS and to maintenance therapy (9) with regard to progression-free survival. Several RCTs have explored the possibility that intensification of chemotherapy beyond hematological limiting toxicity with autologous stem cell rescue (10–13) may improve EFS. With the recent RCTs of chemoimmunotherapy showing an OS benefit (8,14), the impact of any toxic therapy on OS should be questioned. Although narrative reviews are available (3,15–17), to our knowledge, no systematic review and meta-analysis has addressed this issue. Herein, we report the results of a systematic review and meta-analysis of the available RCTs examining the impact of high-dose chemotherapy with autologous stem cell transplantation (ASCT) vs any chemotherapy in the primary management of adults with advanced FL on OS, EFS, treatment-related mortality (TRM),...
incidence of secondary myelodysplasia/acute myeloid leukemia (MDS/AML) and secondary solid tumors. Our main hypothesis is that ASCT improves OS, and previously reported trials may not have enough statistical power to detect differences in survival.

Methods

Search Strategy

Study Selection
We included all RCTs of previously untreated FL adult patients that compared high-dose myeloablative chemotherapy with autologous peripheral blood or bone marrow stem cell transplantation, whether published or unpublished, in any language, which enrolled patients of any histological grade (World Health Organization grades I, II, and III) and clinical risk factors. Acceptable treatment regimens included any form of chemotherapy with or without radiation or immunotherapy during or after chemotherapy. Only trials with available data, either published or retrieved through personal communication, were included in the meta-analysis. Two reviewers (M. Al Khabori, J. R. de Almeida) independently screened all citations. Additional information (gathered from the full text and by contacting the authors) was retrieved for citations that were deemed potentially eligible. Disagreement was resolved by discussion.

Data Abstraction
Two reviewers (M. Al Khabori, J. R. de Almeida) abstracted the data independently using a common data collection form that had been piloted specifically for this review. Any disagreement on the data extracted from the studies was resolved by discussion and review of the full text or the original source. Corresponding authors of all eligible trials were contacted for missing and updated data on OS, EFS, TRM, MDS/AML, secondary malignancies, and questions regarding methodological issues and to confirm results and resolve questions on methodology of the trials. We received further data by personal communication for three trials from Dr C. Sebban (OS, EFS, TRM, method of sequence generation, allocation concealment, and number of patients who were lost to follow-up), Dr M. Ladetto (OS, EFS, TRM, MDS/AML, and secondary malignancies), and Dr Deconinck (OS, EFS, TRM, MDS/AML, solid tumor incidence, method of sequence generation, allocation concealment, and number of patients who were lost to follow-up).

Risk of Bias Assessment
The two reviewers independently abstracted information from six design elements related to risk of bias, including sequence generation, concealment of allocation, blinding, completeness of follow-up, selective reporting and other biases using categories of low, unclear, and high risk (18). We calculated the Cohen kappa coefficient (κ) to assess the agreement between the two reviewers.

CONTEXT AND CAVEATS

Prior knowledge
Different chemotherapies have been combined with autologous stem cell transplantation (ASCT) in randomized clinical trials for follicular lymphoma, a type of non-Hodgkin lymphoma. The effect of these combinations on event-free survival varies, and a comparison of the survival benefits elicited by these different immune-chemotherapies has not been reported.

Study design
A systematic review and meta-analysis of randomized control trials comparing chemotherapy alone with chemotherapy and ASCT for follicular lymphoma were performed. Overall survival, event-free survival, and other adverse patient outcomes were compared for patients who received chemotherapy alone vs chemotherapy with ASCT. The quality of evidence for each analysis was also assessed.

Contribution
Seven randomized clinical trials met the predetermined eligibility criteria. Moderate quality evidence of three trials that reported overall survival indicated that high-dose chemotherapy with ASCT did not improve the overall survival of adult follicular lymphoma patients. On the basis of low-quality evidence from four trials, event-free survival was longer for patients who received chemotherapy with ASCT. Other adverse outcomes and the absolute risk of death from treatment did not differ between the two treatment arms.

Implications
Long-term follow-up of patients in trials is needed to better assess the effect of ASCT on event-free survival. Future clinical trials measuring the effect of combining ASCT with high-dose chemotherapy on overall survival are needed.

Limitations
Because of low-quality evidence, the suggested improvement in event-free survival for patients treated with chemotherapy, and ASCT should be investigated in additional trials with longer follow-up. Some data from unpublished trials were unavailable for analysis and may have led to potential publication bias.

From the Editors
when categorizing the six elements and reported it as overall agreement. Any disagreement on the quality rating between the two reviewers was resolved by discussion and consensus. The lack of blinding was not considered to result in a high risk of bias, given the objective nature of the outcomes used in this systematic review (OS, EFS, TRM, MDS/AML, and secondary malignancies).

Outcome Measures
OS and EFS were defined according to the International Workshop criteria (19). OS was defined for all patients from the date of entry into the trial to the time of death from any cause. For patients with complete and partial response to chemotherapy, EFS was defined as the date of entry into the trial until death from any cause or progression of disease. We also reported definitions by authors not using the International Workshop criteria (19). TRM was defined as deaths related to chemotherapy or ASCT within 1 year of completion of treatment. Secondary malignancies were defined as any MDS, AML, or solid tumors that developed after chemotherapy or ASCT.

Analysis and Data Synthesis
For binary outcomes, the treatment effect was expressed as relative risk (RR) with its 95% confidence interval (CI). For the time to event outcomes, the treatment effect is expressed as hazard ratio (HR) with its 95% confidence interval. If the hazard ratio is not reported in the article and no information could be collected from the primary authors, we used Parmar methods (20,21) to estimate the hazard ratio from the available data. Cohen kappa coefficient (22) was calculated to measure the agreement between the two reviewers (M. Al Khabori, J. R. de Almeida) on the relevant studies identified at the screening and full text stages. All meta-analyses used random effect models. Heterogeneity was assessed by Cochrane $\chi^2$ analysis and by measuring $I^2$. We explored the following a priori hypotheses to explain heterogeneity: baseline risk [high risk defined as ≥3 factors on the FLIPLI or IPS (24,25)]; use of rituximab; follow-up (≤5 vs >5 years); and type of analysis (intention-to-treat and per protocol). For the baseline risk, the subgroup analysis of interest was not reported in the published trials; therefore, we were only able to conduct the subgroup comparison between trials. Trials with high-risk patients compromising more than a third of the study population were considered as high risk. For the OS and EFS outcomes, we expected the benefit of ASCT to be greater in high-risk patients and in per protocol analyses and lower with use of rituximab and longer follow-up. For the TRM, MDS/AML, and secondary malignancy outcomes, we expected higher event rates with longer follow-up. Other analyses and $\chi^2$ tests of subgroup interaction were performed using RevMan 5 (Review Manager 5 computer program, version 5.0. Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2008) according to methods described by Deeks et al. (26). The GRADE criteria (27) were used to summarize the evidence gathered in the systematic review for each outcome in the following domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The results were presented in an evidence profile. All statistical tests were two-sided and carried out at $\alpha = .05$. The $P$ value for comparing heterogeneity between subgroups was calculated using Cochrane $\chi^2$ (23).

Results
Search Results
The search strategy identified 1661 citations (Figure 1). After screening titles and abstracts, 1625 were excluded for the following reasons: duplicate publications, not RCT, and disease not FL. Full text or further details were retrieved for the remaining 36 citations. Of those, 23 duplicate reports and six non-RCT studies were excluded. Three RCTs (28–30) included in the systematic review did not have data available for pooling and were excluded from this meta-analysis. The $k$ statistics for the agreement between the two reviewers (M. Al Khabori, J. R. de Almeida) for the screening stage and the full text stage of the search were 0.72 and 0.82, respectively.

Characteristics of the Included Studies
Seven RCTs were identified (Table 1) and included in the systematic review, but only four RCTs with data from 941 patients were included in this meta-analysis (11–13,31) (Table 2), as outcome data were not available for pooling from three of the trials. All trials were multicenter (information was not available for Portlock, NCI-V89-0192), two-arm, parallel prospective RCTs. The sample sizes ranged from 67 (30) to 469 (29) adult participants with previously untreated FL. In the four trials with available data, the median age was approximately 50 years. High-risk patients constituted less than a third of the patients enrolled except in one trial (11) in which they represented 58% of the population. A variety of induction, mobilization, and high-dose therapy regimens were used in the transplant and chemotherapy arms of the four trials, as detailed in Table 1. In two of the trials, patients in both arms received rituximab during the induction treatment (11,30). The median follow-up duration was up to 5 years for two trials (11,12) and approximately 9 years for the other two trials (13,31). OS was
Table 1. Description of randomized clinical trials included in the systematic review*

<table>
<thead>
<tr>
<th>First author, year published (reference)</th>
<th>Design</th>
<th>No. of patients</th>
<th>Trial description</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenz et al. 2004 (12)</td>
<td>Multicenter two arms parallel prospective controlled</td>
<td>240</td>
<td>Initial treatment: two cycles of CHOP or MCP chemotherapy. Two further cycles if not in CR. Mobilization: Dexa-BEAM. High-dose chemotherapy: combined total body irradiation (12 Gy in six applications) and cyclophosphamide (60 mg/kg body weight, i.v., on days −3 and −2).</td>
<td>Initial treatment: four cycles of CHOP or MCP chemotherapy. Two further cycles if not in CR. All treatments are supplemented by two extra cycles to balance mobilization of chemotherapy in the other arm. Maintenance: subcutaneous IFN-α (5 mU) was administered three times weekly until disease progression was observed.</td>
</tr>
<tr>
<td>Deconinck et al. 2005 (10)</td>
<td>Multicenter two arms parallel prospective controlled</td>
<td>166</td>
<td>Initial treatment: VCAP regimen was administered every 3 wk. For patients in CR, VGPR, or PR after the second or third cycle VCAP, they continued stem cell harvesting. Before transplantation, patients received one course of IMVP16. Patients with less than PR after the VCAP chemotherapy received salvage therapy of two to three courses of DHAP. If at least a PR was obtained after DHAP, stem cells were harvested; otherwise patients went off study. High-dose chemotherapy: combined total body irradiation (12 Gy in six applications) and cyclophosphamide (60 mg/kg for 2 d).</td>
<td>Initial treatment: a six-course induction phase of CHVP regimen was administered monthly. This is followed, for responders and patients presenting with stable disease, by a maintenance phase that consisted of one cycle every 2 mo for 1 y. Concomitant subcutaneous IFNα2b was administered at 5 mU three times per week for 18 mo.</td>
</tr>
<tr>
<td>Sebban et al. 2006 (13)</td>
<td>Multicenter two arms parallel prospective controlled</td>
<td>401</td>
<td>Initial treatment: CHOP chemotherapy was administered every 3 wk for four cycles. Mobilization: responding patients (CR or PR) received a single course of cyclophosphamide (4500 mg/m²), etoposide (450 mg/m²), and granulocyte-colony-stimulation factor (300 µg) from days 4–12 followed by peripheral blood stem cell harvest. High-dose chemotherapy: cyclophosphamide (60 mg/kg/d) and etoposide (150 mg/m²) were administered from day −6 to −5. Total body irradiation was then performed delivering 10 Gy in five fractions.</td>
<td>Initial treatment: CHVP chemotherapy was administered for six cycles. During the study, teniposide was replaced by etoposide (100 mg/m²) on day 1. IFNα was given subcutaneously at a dosage of 5 mU three times a week. Patients achieving a CR or PR received six courses of CHVP plus IFNα every 2 mo for 1 y.</td>
</tr>
<tr>
<td>Ladetto et al. 2008 (11)</td>
<td>Multicenter two arms parallel prospective controlled</td>
<td>134</td>
<td>Initial treatment: doxorubicin, vincristine, prednisone chemotherapy, totaling four 75 mg/m² doxorubicin administrations, was given. Patients not achieving CR received two additional DHAP treatments. Mobilization: etoposide (2 g/m²) was administered followed by a chemotherapy-free interval of 40 d during which patients received two courses of rituximab (375 mg/m²). Cyclophosphamide (7 g/m²) was then delivered. Two further rituximab doses were given on the day after cyclophosphamide administration and on the first day the patient had a whole blood cell count greater than 1000 per µL for the in vivo purging. Patients in PR or who remained PCR positive received two final rituximab courses at the end of the program. High-dose chemotherapy: mitoxantrone (60 mg/m²) on day −5 and melphalan (180 mg/m²) on day −2. Radiation therapy included 30–36 Gy on bulky sites or on residual masses 2 mo after finishing the treatment.</td>
<td></td>
</tr>
</tbody>
</table>

(Table continues)
reported by three trials (11,13,31). The trial described by Lenz et al. (12) did not report OS, and the author did not provide the data. EFS was reported for three trials (11,13,31) with definitions consistent with that of the International Workshop criteria (19). In the study reported by Lenz et al. (12), only progression-free survival was reported as the disease control outcome.

Two (28,29) of three RCTs with no available data were found on the National Cancer Institute website (www.cancer.gov): Portlock (NCI-V89-0192) and the European Organization for Research and Treatment of Cancer (NCT00003152). These studies started in 1990 and 1997, respectively, and both terminated enrollment. Available details of the design and interventions are presented in Table 1. The study by Portlock (NCI-V89-0192) planned to include 106 patients with non-Hodgkin lymphoma (stage 3 or 4) in complete remission following ProMACEMOPP chemotherapy (cyclophosphamide, doxorubicin, etoposide, mustargen, oncovirin, procarbazine, and prednisone). The NCT00003152 study planned to include 469 patients with advanced FL (stage 3 or 4) in partial or complete remission after eight 3-weekly courses of CVP chemotherapy (cyclophosphamide, vincristine, and prednisone). Both studies have not been published, and further information could not be retrieved from the corresponding investigators. The results of the third trial, reported by Meckenstock et al. (30), were reported at an interim analysis in a conference abstract. The available data on the patients and interventions are detailed in Table 1, although no further information could be retrieved from the corresponding author. Participants were adults aged less than 60 years with advanced FL. With a median follow-up of 23 months, both the EFS and OS were similar between the two arms (64 evaluable patients of 67 total enrolled).

### Risk of Bias

Two reviewers (M. Al Khabori, J. R. de Almeida) independently assessed the reports with a very good overall agreement ($\kappa = 0.72$). The lowest agreement was in the other bias category in which either reviewer felt that limited reporting of quality domains might have biased the results. Of four trials with available data (11–13,31), one trial reported their sequence generation (11) and two others provided sequence generation by personal communication (13,31); all were computer generated and consistent with low risk of bias.

Allocation concealment (central randomization) was reported by the four trials (11–13,31). Patients and physicians were not blinded in any of the trials and it was not stated (not available through personal communication), if blinding was used at the time of data collection, analysis, or article preparation. Only the trial reported by Ladetto et al. (11) specifically stated the loss to follow-up and methods used to deal with the loss to follow-up. All trials performed the analysis as intention to treat except for one trial (12) in which analysis was reported as per protocol, although $P$ was stated for the intention-to-treat analysis. One trial (11) was stopped early because benefit in EFS favoring ASCT was observed.

### Outcomes

The three studies that reported OS (11,13,31) enrolled 701 patients and reported no statistically significant difference in OS (a pooled HR of OS = 0.99, 95% CI = 0.73 to 1.33, $I^2 = 25\%$; $F = 0\%$, 95% CI for $F = 0\%$ to 90%) (Table 3 and Figure 2). The
Table 2. Patient characteristics of published autologous stem cell transplant studies included in the meta-analysis*

<table>
<thead>
<tr>
<th>First author, year published (reference)</th>
<th>Total No. of patients (men, women)</th>
<th>Median age, y (range)</th>
<th>No. of high-risk patients (%)</th>
<th>No. of patients with B symptoms (%)†</th>
<th>No. of patients with poor performance status (%)‡</th>
<th>No. of patients with bulky disease (%)</th>
<th>Stem cell harvest</th>
<th>Study sponsor(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenz, 2004 (12)§</td>
<td>240 (118, 122)</td>
<td>49.1 (29–59)</td>
<td>41 (17.1)</td>
<td>87 (36.3)</td>
<td>13 (5.4)</td>
<td>NR</td>
<td>At least $2 \times 10^6$ CD34$^+$ cells per kg of body weight (and $2 \times 10^6$ CD34$^+$ cells per kg body weight as backup) were required.</td>
<td>Supported in part by a grant of the Deutsche Krebshilfe (project number 70-2208-Hi 2)</td>
</tr>
<tr>
<td>Deconinck, 2005 (10)ǁ</td>
<td>166 (85, 81)</td>
<td>51 and 50 (29–61)</td>
<td>NR</td>
<td>46 (27.7)</td>
<td>10 (6.0)</td>
<td>53 (31.9)</td>
<td>NR</td>
<td>French Ministere de la Sante et de la Solidarite Sociale and the Schering-Plough.</td>
</tr>
<tr>
<td>Sebban, 2006 (13)#</td>
<td>401 (221, 180)</td>
<td>49</td>
<td>120 (29.9)</td>
<td>102 (25.4)</td>
<td>29 (7.2)</td>
<td>266 (66.3)</td>
<td>$4 \times 10^9$ mononuclear cells per kg of body weight were required.</td>
<td>French Programme Hospitalier de Recherche Clinique (PHCRC-1994) and by a grant from Schering-Plough, Roche (Milan, Italy), Compagnia di San Paolo (Torino, Italy), Ministero Italiano Universita e Ricerca (Rome, Italy), and Regione Piemonte (Torino, Italy)</td>
</tr>
<tr>
<td>Ladetto, 2008 (11)**</td>
<td>134 (78, 56)</td>
<td>51 (25–59)</td>
<td>78 (58.2)</td>
<td>63 (47.0)</td>
<td>80 (59.7)</td>
<td>75 (55.9)</td>
<td>A minimum of $5 \times 10^6$ CD34$^+$ cells per kg of body weight was required for autologous transplantation with PBSCs only (plus at least $3 \times 10^6$ CD34$^+$ cells per kg of body weight or a bone marrow harvest as backup) were required.</td>
<td>Roche (Milan, Italy), Compagnia di San Paolo (Torino, Italy), Ministero Italiano Universita e Ricerca (Rome, Italy), and Regione Piemonte (Torino, Italy)</td>
</tr>
</tbody>
</table>

* NR = not reported; PBSC = peripheral blood stem cells.
† Fever >38°C, weight loss, night sweats.
‡ Patients with an Eastern Cooperative Oncology Group score of 2 or more were designated as having poor performance status.
§ Patients with an International Prognostic Index or Follicular Lymphoma International Prognostic Index score of greater than 2 were designated high risk.
ǁ Median age of patients was 51 years for the transplant arm and 50 years for the chemotherapy arm. For this study, patients with a Follicular Lymphoma International Prognostic Index score of greater than 2 were designated high risk.
# For this study, bulky disease was defined as tumors greater than 7 cm in diameter.
** For this study, bulky disease was defined as tumors greater than 5 cm in diameter.
Table 3. Evidence profile of autologous stem cell transplantation studies used for meta-analysis*

<table>
<thead>
<tr>
<th>Study characteristics</th>
<th>Data quality assessment</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Estimation of absolute event rates (derived from observed events in study)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Event rate with chemotherapy only</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not available</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of study</th>
<th>No. of studies</th>
<th>No. of patients</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Publication bias</th>
<th>Relative effect† (95% CI)</th>
<th>Event rate with chemotherapy only</th>
<th>Event rate with ASCT (95% CI)</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>3</td>
<td>701</td>
<td>No serious limitations, one RCT stopped early for EFS benefit</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise (95% CI includes important benefit and harm)</td>
<td>Unlikely (tends to bias toward positive)</td>
<td>HR = 0.99 (0.73 to 1.33)</td>
<td>Not available</td>
<td>Not available</td>
<td>Moderate (imprecision)</td>
</tr>
<tr>
<td>EFS</td>
<td>4</td>
<td>941</td>
<td>Serious limitation, one study stopped early, another study PP</td>
<td>Inconsistent (explained by a priori hypotheses)</td>
<td>Direct</td>
<td>Precise</td>
<td>Likely</td>
<td>HR = 0.54 (0.36 to 0.82)</td>
<td>Not available</td>
<td>Not available</td>
<td>Low (inconsistency, risk of bias, publication bias)</td>
</tr>
<tr>
<td>Treatment-related mortality</td>
<td>3</td>
<td>701</td>
<td>Serious limitation, one RCT stopped early</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise (95% CI includes benefit and harm)</td>
<td>Likely</td>
<td>RR = 1.04 (0.29 to 3.70)</td>
<td>14 per 1000</td>
<td>15 per 1000 (4 to 52)</td>
<td>Low (imprecision, risk of bias, likely publication bias)</td>
</tr>
<tr>
<td>MDS/AML</td>
<td>3</td>
<td>701</td>
<td>Serious limitation, one study stopped early</td>
<td>Inconsistent (inconsistency not fully explained by a priori hypotheses)</td>
<td>Direct</td>
<td>Imprecise (95% CI includes benefit and harm)</td>
<td>Unlikely</td>
<td>RR = 2.19 (0.45 to 10.55)</td>
<td>17 per 1000</td>
<td>37 per 1000 (8 to 170)</td>
<td>Low (inconsistency, imprecision, risk of bias)</td>
</tr>
<tr>
<td>Secondary solid tumors</td>
<td>3</td>
<td>701</td>
<td>Serious limitation, one study stopped early</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise (95% CI includes benefit and harm)</td>
<td>Unlikely</td>
<td>RR = 1.30 (0.33 to 5.08)</td>
<td>34 per 1000</td>
<td>44 per 1000 (11 to 173)</td>
<td>Low (risk of bias, imprecision)</td>
</tr>
</tbody>
</table>

* ASCT = autologous stem cell transplantation; CI = confidence interval; CR = complete response; EFS = event-free survival; HR = hazard ratio; MDS/AML = secondary myelodysplasia/acute myeloid leukemia; PP = per protocol; RCT = randomized controlled trial; RR = relative risk.
† The pooled survival probability for the chemotherapy arm across all studies is not available given the lack of individual patient data.
quality of evidence was rated moderate because of imprecision (Table 3). Also, an estimation of the absolute event rates (derived from observed events in the study) for patients who received chemotherapy only and ASCT were unavailable (Table 3).

All four trials, with a total of 941 patients, suggested an improvement in EFS in favor of ASCT (11–13, 31) (pooled HR of EFS = 0.54, 95% CI = 0.36 to 0.82; I² heterogeneity = 002; F = 80%, 95% CI for F = 48% to 93%) (Figure 3). This heterogeneity was because of the duration of follow-up and a statistically significant subgroup effect (P < .001). The median follow-up was 4–5 years for two trials (11, 32) (pooled HR of the two trials = 0.38, 95% CI = 0.28 to 0.52, F = 0%) and 9 years for the other two (13, 31) (pooled HR for the two trials = 0.77, 95% CI = 0.61 to 0.97, F = 14%) (Figure 3). Comparing the trial using rituximab as part of the initial therapy vs those that did not, the EFS was statistically significantly decreased (HR of trials with rituximab = 0.38, 95% CI = 0.25 to 0.59 vs pooled HR of trials not employing rituximab = 0.60, 95% CI = 0.38 to 0.95; F = 79%; P for subgroup effect = .02). The quality of evidence (27) was rated low because of inconsistency, early termination, and potential publication bias (Table 3).

Three studies reported TRM (11, 13, 31) with five treatment-related deaths among 346 patients who underwent ASCT and five deaths among 355 patients who received chemotherapy. The difference in TRM between the two arms was not statistically significant (pooled RR = 1.04, 95% CI = 0.29 to 3.70, I² heterogeneity = 51; F = 0%, 95% CI for F = 0% to 90%). The absolute risk across the chemotherapy arms was 14 deaths per 1000 patients, whereas the calculated absolute risk with ASCT on the basis of the above relative risk is 15 in 1000 (range = 4–52 deaths per 1000 patients). The quality of evidence (27) was rated low because of imprecision, early termination of one RCT, and potential publication bias (Table 3).

Data regarding the development of MDS/AML were reported for three trials (11–13, 31). In the transplant arm, 13 of 346 patients developed MDS/AML during follow-up compared with six of 355 patients in the chemotherapy arm. The difference in MDS/AML rates between the two arms was not statistically significant (pooled RR = 2.19, 95% CI = 0.45 to 10.55, I² heterogeneity = 54; F = 48%, 95% CI for F = 0% to 85%) (Figure 4). The absolute risk across the chemotherapy arms was 17 in 1000, whereas the calculated absolute risk with ASCT strategy on the basis of the above

### Table 3. Forest plot of overall survival. F was calculated according to the method described by Deeks et al. (23). The first author, year of publication, and reference are given for each study. The hazard ratios (boxes) with 95% confidence intervals (CIs, horizontal lines) were calculated, and the pooled hazard ratio (diamond) was estimated with generic inverse variance (IV) using random effect analysis. The weight of each study’s contribution to the overall effect calculated from random effect analysis is given and also reflected by the size of the box. All statistical tests were two-sided. The P value for comparing heterogeneity between subgroups was calculated using Cochrane χ² (23). ASCT = autologous stem cell transplantation; chemo = chemotherapy.
relative risk is 37 deaths in 1000 patients (range = 8–170 in 1000). Most of the heterogeneity was created by the study reported by Sebban et al. (13). Baseline risk, use of rituximab, or follow-up duration did not explain this heterogeneity (for all analyses, $I^2 = 32$). The quality of evidence (27) was rated as low because of inconsistency, imprecision, and early termination of one RCT (Table 3).

Three trials (11,13,31) reported data on solid tumors. There were 16 and 12 solid tumors, respectively, observed in a sample of 346 ASCT patients and 355 standard-dose therapy patients. The solid tumor rates for the two treatment arms were similar (pooled RR for second solid tumors = 1.30, 95% CI = 0.33 to 5.08, $P_{\text{heterogeneity}} = 20$; $F = 38\%$, 95% CI for $F = 0\%$ to 81%). The absolute risk across the chemotherapy arms was 34 in 1000 patients, whereas the calculated absolute risk with ASCT strategy on the basis of the above relative risk is 44 in 1000 (range = 11–173 in 1000). The quality of evidence (27) was rated low because of imprecision and early termination of one RCT (Table 3).

Discussion

In this systematic review and meta-analysis, we found moderate quality evidence that high-dose chemotherapy and ASCT did not improve OS in adults with previously untreated FL. EFS was superior for the transplant arm compared with the chemotherapy arm, albeit with substantial heterogeneity. This survival benefit comes at the expense of MDS/AML at a relative risk that cannot exclude a large increase risk in the transplant arm. The TRM and rates of secondary solid tumors were similar between those who received chemotherapy only vs ASCT.

The estimate of the hazard ratio for OS was rated moderate on evidence quality because of imprecision. Although OS comparisons were not reported in all of the trials, we do not anticipate publication bias as this would likely bias the pooled estimate toward a positive treatment effect. Use of immunoimmunotherapy including rituximab in subsequent treatment for the non-transplanted patients may have contributed to the lack of survival difference (9). The higher rate of MDS/AML in the transplant arm in trials with longer follow-up may contribute to the lack of a difference in survival that was observed.

The EFS was rated low on evidence quality on the basis of the inconsistency, per protocol analysis used by one of the studies contributing to the pooled estimate (12), and the likelihood of publication bias. Three trials (28–30) found through the systematic search had no published data and were not included in the meta-analysis. One of the three excluded trials showed lack of benefit of the transplantation strategy in an interim analysis (30). This publication bias may have biased the results toward benefit and, if included, could change the pooled estimate toward no difference or even harm. In our review, we pooled the hazard ratios of progression-free survival reported by Lenz et al. (12) with hazard ratios of EFS from the other trails. Pooling hazard ratios of progression-free survival with hazard ratios of EFS would likely increase the apparent statistical significance of the difference in EFS and for our study, bias the pooled hazard ratio in favor of the ASCT assuming similar induction failures in both treatment arms.

Although the heterogeneity in the EFS was substantial, it could be explained by the duration of follow-up. This subgroup analysis suggests that on long-term follow-up, the treatment effect disappears. Although this subgroup analysis was between trials, it was planned a priori, and likely represents a true subgroup effect (33). Furthermore, it is consistent with the natural history of this indolent lymphoma (16) and the tendency for patients to experience multiple relapses. No curative treatments are available, except for a highly selected group receiving allogeneic stem cell transplantation (34).

The serious methodological limitations (early termination and per protocol analysis) along with the imprecision and the likelihood of publication bias resulted in a low evidence quality rating for TRM. The MDS/AML outcome was also rated low for the inconsistency and the limitation of early termination of one trial. None of the a priori hypotheses to explore heterogeneity explained this inconsistency. The pooled estimate with the 95% confidence interval suggests large potential harm that may be introduced by ASCT, although it also includes the small potential harm of chemotherapy.

Because the introduction of monoclonal antibody therapy for indolent lymphoma is relatively recent, only two trials (11,30) used rituximab as part of their treatment in all patients in both treatment arms. The relevance of any conclusions regarding the
effectiveness of therapy intensification with ASCT in light of the evolution of the standard of care for FL remains limited given the survival benefit shown with adding rituximab to chemotherapy (35). For example, the median time to progression was 32 months after rituximab-containing chemotherapy vs 15 months for chemotherapy alone (P < .001) in a landmark clinical trial (35). In addition, maintenance rituximab improves the median progression-free survival compared with observation (51.5 months for rituximab vs 14.9 months for observation, P < .001), as shown in relapse-refractory settings (14). The subgroup effect of trials using rituximab in our analysis suggests that use of rituximab has a synergistic effect when combined with high-dose chemotherapy and ASCT. The interpretation of this finding is limited by the publication bias of at least one other trial (30) that used rituximab and found a non-statistically significant difference.

There are a number of limitations associated with our systematic review and meta-analysis. The lack of complete data from unpublished trials may have led to a potential publication bias. Trials with no statistically significant treatment effect or those that stopped early because of toxic effects in the ASCT arm are more likely not to be published. This tendency would bias EFS toward an apparent benefit. No formal test of publication bias was done because of the small number of studies analyzed. The other limitation was the power, especially in the OS outcome. With a pooled sample size of 701 patients, we have 80% power to detect a minimum treatment effect (HR = 0.65) using a two-sided alpha of 0.05 (36). Therefore, one cannot rule out a smaller effect size than that of a hazard ratio of 0.65. Finally, the subgroup analyses were done comparing treatment effects between trials and not within trials as those subgroup analyses were not reported for each trial.

The current systematic review and meta-analysis showed no benefit for high-dose chemotherapy and ASCT in OS for patients with previously untreated FL. Long-term follow-up is needed from clinical trials to better estimate the impact of ASCT on EFS and the risk of secondary MDS/AML. In addition, data from the unpublished trials should be made available for a more complete assessment of the treatment effect, and to guide the development of future clinical trials. Trials of ASCT in the context of current chemoimmunotherapy approaches in FL are needed to further evaluate the ability of intensification of therapy using ASCT to improve OS.

References


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