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High-dose therapy with autologous stem cell transplantation versus chemotherapy or immuno-chemotherapy for follicular lymphoma in adults (Review)

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[Intervention Review]

High-dose therapy with autologous stem cell transplantation versus chemotherapy or immuno-chemotherapy for follicular lymphoma in adults

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ABSTRACT

Background

Follicular lymphoma (FL) is the most common indolent and second most common Non-Hodgkin`s lymphoma (NHL) in the Western world. Standard treatment usually includes rituximab and chemotherapy. High-dose therapy (HDT) followed by autologous stem cell transplantation (ASCT) is an option for patients in advanced stages or for second-line therapy, leading to improved progression-free survival (PFS) rates. However, the impact of HDT and ASCT remains unclear, as there are hints of an increased risk of second cancers.

Objectives

We performed a systematic review with meta-analysis of randomised controlled trials (RCTs) comparing HDT plus ASCT with chemotherapy or immuno-chemotherapy in patients with FL with respect to overall survival (OS), PFS, treatment-related mortality (TRM), adverse events and secondary malignancies.

Search methods

We searched CENTRAL, MEDLINE, and EMBASE as well as conference proceedings from January 1985 to September 2011 for RCTs. Two review authors independently screened search results.

Selection criteria

Randomised controlled trials comparing chemotherapy or immuno-chemotherapy with HDT followed by ASCT in adults with previously untreated or relapsed FL.

Data collection and analysis

We used hazard ratios (HR) as effect measures used for OS and PFS as well as relative risks for response rates. Two review authors independently extracted data and assessed the quality of trials.

Main results

Our search strategies led to 3046 potentially relevant references. Of these, five RCTs involving 1093 patients were included; four trials in previously untreated patients and one trial in relapsed patients. Overall, the quality of the five trials is judged to be moderate. All trials were reported as randomised and judged to be open-label studies, because usually trials evaluating stem cell transplantation are not blinded.

Due to the small number of studies in each analysis (four or less), the quantification of heterogeneity was not reliable and not evaluated in further detail. A potential source of bias are uncertainties in the HR calculation. For OS, the HR had to be calculated for three trials from survival curves, for PFS for two trials.

We found a statistically significant increased PFS in previously untreated FL patients in the HDT + ASCT arm (HR = 0.42 (95% confidence interval (CI) 0.33 to 0.54; P < 0.00001). However, this effect is not transferred into a statistically significant OS advantage (HR = 0.97; 95% 0.76 to 1.24; P = 0.81). The subgroup of trials adding rituximab to both intervention arms (one trial) confirms these results and the trial had to be stopped early after an interim analysis due to a statistically significant PFS advantage in the HDT + ASCT arm (PFS: HR = 0.36; 95% CI 0.23 to 0.55; OS: HR = 0.88; 95% CI 0.40 to 1.92). In the four trials in previously untreated patients there are no statistically significant differences between HDT + ASCT and the control-arm in terms of TRM (RR = 1.28; 95% CI 0.25 to 6.61; P = 0.77), secondary acute myeloid leukaemia/ myelodysplastic syndromes (RR = 2.87; 95% CI 0.7 to 11.75; P = 0.14) or solid cancers (RR = 1.20; 95% CI 0.25 to 5.77; P = 0.82). Adverse events were rarely reported and were observed more frequently in patients undergoing HDT + ASCT (mostly infections and haematological toxicity).

For patients with relapsed FL, there is some evidence (one trial, N = 70) that HDT + ASCT is advantageous in terms of PFS and OS (PFS: HR = 0.30; 95% CI 0.15 to 0.61; OS: HR = 0.40; 95% CI 0.18 to 0.89). For this trial, no results were reported for TRM, adverse events or secondary cancers.

Authors' conclusions

In summary, the currently available evidence suggests a strong PFS benefit for HDT + ASCT compared with chemotherapy or immuno-chemotherapy in previously untreated patients with FL. No statistically significant differences in terms of OS, TRM and secondary cancers were detected. These effects are confirmed in a subgroup analysis (one trial) adding rituximab to both treatment arms. Further trials evaluating this approach are needed to determine this effect more precisely in the era of rituximab. Moreover, longer follow-up data are necessary to find out whether the PFS advantage will translate into an OS advantage in previously untreated patients with FL.

There is evidence that HDT + ASCT is advantageous in patients with relapsed FL.

PLAIN LANGUAGE SUMMARY

Treatment of follicular lymphoma

Follicular lymphoma is a malignancy of the lymphatic system and a common type of non-Hodgkin lymphoma. Follicular lymphoma arises from B-cells, mainly affects older adults and because of its slow growth it is called an indolent lymphoma. Follicular lymphoma grows unnoticed for a long time and is recognised by lymph node enlargement, fever, weight loss, sweating or fatigue. It is called follicular lymphoma because affected lymph nodes show rounded structures called "follicles". Using computer tomography scans, bone marrow biopsy and blood tests, follicular lymphoma is classified into the early Ann Arbor stages I and II or the advanced Ann Arbor stages III or IV, which are diagnosed in the majority of patients. Prognosis and therapy are related to the extent of the disease at initial diagnosis. The small number of patients in stages I or II may be cured by radiotherapy. In advanced stages III or IV, patients are regarded as incurable. Chemotherapy plus the monoclonal antibody rituximab is considered as current treatment strategy for symptomatic patients in advanced stages. Positive effects of high-dose therapy with transplantation of patients' own stem cells (autologous) are known for patients in advanced stages, especially for the endpoint progression-free survival. However, this treatment option could have comparatively more treatment-related late side effects than chemotherapy, including secondary malignancies.

With this assumption, we assessed the role of high-dose therapy followed by autologous stem cell transplantation in the treatment of follicular lymphoma in adults. We included five trials with 1093 patients in the main analyses. As a result, the meta-analyses for previously untreated patients (four trials) show no statistical significant differences in terms of survival, treatment-related mortality or secondary malignancies between the patients treated with high-dose therapy followed by autologous stem cell transplantation and those treated with chemotherapy only. However, progression-free survival (tumour control), was significantly improved by the high-dose chemotherapy and stem cell transplantation. Adverse events are more common in patients treated with high-dose therapy followed by autologous stem cell transplantation.

There is an advantage of the high-dose chemotherapy and stem cell transplantation for patients with a relapse of the disease, both in survival and in tumour control (one trial). No data on adverse events are reported in this trial.

Summary of findings for the main comparison.

High-dose chemotherapy plus ASCT versus chemotherapy for adult previously untreated patients with follicular lymphoma

Patient or population: Adult patients with follicular lymphoma

Intervention: High-dose chemotherapy plus ASCT

Comparison: Chemotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	High-dose chemotherapy plus ASCT				
Overall survival Follow-up: median 5 years	**Moderate risk population** [2]		**HR 0.97** (0.76 to 1.22)	701 (3 studies)	⊕⊕⊕⊖ **moderate** [1]	
	200 per 1000	**195 per 1000** (125 to 235)				
Treatment-related mortality	**Study population**		**RR 1.28** (0.25 to 6.61)	941 (4 studies)	⊕⊕⊕⊖ **moderate**[3]	
	12 per 1000	**16 per 1000** (3 to 82)				
	Moderate risk population					
	11 per 1000	**14 per 1000** (3 to 73)				
Progression-free survival Follow-up: mean 5 years	**Low risk population**		**HR 0.42** (0.33 to 0.54)	540 (3 studies)	⊕⊕⊕⊖ **moderate**[4]	
	560 per 1000	**297 per 1000** (237 to 538)				
	High risk population					
	880 per 1000	**598 per 1000** (503 to 682)				

Secondary malignancies **AML/MDS**	**Study population**		**RR 2.87** (0.7 to 11.75)	1023 (4 studies)	⊕⊕⊝⊝ **low**[1,3]	As all trials had a median observation time of less than 10 years, long-term information on secondary malignancies cannot be expected.
	11 per 1000	**32 per 1000** (8 to 132)				
	Medium risk population					
	14 per 1000	**40 per 1000** (10 to 164)				
Secondary malignancies **Solid cancer**	**Study population**		**RR 1.2** (0.25 to 5.77)	701 (3 studies)	⊕⊕⊝⊝ **low**[1,3]	As all trials had a median observation time of less than 10 years, long-term information on secondary malignancies cannot be expected.
	37 per 1000	**44 per 1000** (9 to 211)				
	Medium risk population					
	46 per 1000	**55 per 1000** (11 to 265)				
Adverse events	see comment		Not estimable	527 (3 studies)	⊕⊝⊝⊝ **very low** [1,2]	Acute adverse effects were seldom reported and differ across the three reporting studies. They are higher in the HDT + ASCT arm (haematological, non-haematological, infection, see Table 1)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio; **HR**: Hazard Ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] There might be some heterogeneity between trials.
[2] The risk for the low risk population (of patients with follicular lymphoma) was taken from the trial with the highest rates of survival at 5 years (GELF94 trial). The high risk rate is approximately the risk in the CUP-trial, for relapsed patients.
[3] No precise estimation of effect, large confidence interval.
[4] Outcome assessors not blinded. This could cause bias.
[5]Two of the three trials reporting adverse events report a few adverse events only
[6] Two of five trials did not report any adverse event

BACKGROUND

Description of the condition

Follicular lymphoma (FL) is the most common indolent and second most common Non-Hodgkin`s lymphoma (NHL) in the Western world, accounting for > 20% of the approximately 56,000 new cases of NHL in the U.S. yearly (Armitage 1998; Fisher 2004; Jemal 2005; Higgins 2011a). In contrast to other kinds of cancer, the incidence and mortality of this B-cell malignancy rises continuously and has doubled in the last three decades, especially in the U.S. and Europe (Anderson 1998; Groves 2000; Clarke 2002 ; Muller 2005).

The World Health Organization (WHO) divides FL into three major grades based on the number of centroblasts per high-power field (Harris 1999). WHO Grade 1, 2 and 3a correspond to indolent lymphomas. However, the subdivided grade 3b is strictly speaking an aggressive disease and more closely related to diffuse large B-cell lymphoma, the most common highly malignant lymphoma (Ott 2002). Prognosis and therapy of FL are dependent on the respective Ann Arbor stages. Less than 20 % of patients, situated in Ann Arbor I / II, are treated by curative radiotherapy, applied as extended or involved field irradiation (Hiddemann 2006; Lau 2006; Schulz 2007; Brown 2009). All remaining patients diagnosed at advanced-stage disease are regarded as incurable (Andreadis 2005; Foster 2009). In up to 25% to 35% of patients, FL transforms to a high-grade lymphoma with a poor prognosis because of resistance to therapy (Horning 2000). In advanced-stage, FL relapses in shorter intervals, so that concerned patients die after a median survival time of 8 to 10 years because of progressive disease (Horning 1984; Gallagher 1986; Egger 1997; Moher 1999).

Up to 95% of the patients with FL show the translocation t(14;18), which leads to an over-expression of the BCL-2 protein (Korsmeyer 1992). This protein, which has an inhibitory effect on apoptosis (programmed cell death), is a diagnostic help in the differentiation between malignant and reactive follicles (Symmans 1995; Diaz-Alderete 2008). To improve overall survival (OS), different patterns of chemotherapy were prescribed, but these early applied therapies compared with the 'wait and watch' strategy in advanced-stage did not show advantage concerning OS. That is why only symptomatic patients or those with a high tumour burden are treated (Ardeshna 2003). The natural history of FL includes a high initial rate of response to chemotherapy and radiotherapy. In the past, conventional chemotherapy regimens consisting of single and multiple drug alkylating agent-based therapies were used in primary treatment for patients with advanced-stage FL. Despite various chemotherapy combinations in the last decade, no improvement of OS was achieved (Oliansky 2010). Compared with different patterns of chemotherapy such as alkylating agent-based or anthracycline-containing regimens, which did not exceed a median response duration of 1.5 to 3 years despite a response rate of 60% to 70%, Rohatiner et al showed, that chemotherapy combined with interferon α were superior with regard to prolonged OS (Brandt 2001; Reiser 2002; Rohatiner 2005). The status of interferon as maintenance therapy for patients with FL remains unclear, although a progression-free survival (PFS) advantage is reported in a systematic review (Baldo 2010). In the review, interferon was associated with significant toxicities that may have an impact on a patient's quality of life.

In the last few years, progress in the therapy of FL has been recorded (Herold 2007). Monoclonal antibodies, especially rituximab, have shown a proven activity in the therapy of FL and NHL, in salvage therapy as well as in therapy for relapsed FL (Schulz 2007; Vidal 2009).

Description of the intervention

In spite of initially high response rates, FL is usually not curable so that all patients will suffer a relapse (Buske 2007). Non-myeloablative allogeneic stem cell transplantation is a potentially curative treatment option, but long-term effectiveness and toxicity of this strategy are unknown, although there are early promising results in a non-randomised trial (Khouri 2008). Another potentially curative therapy is high-dose therapy (HDT) with autologous stem cell transplantation (ASCT) (Buske 2005). This regimen has been compared with conventional regimens of chemotherapy, primarily in relapsed FL, later on in first remission. Although randomised trials show promising results concerning prolongation of response duration and relapse rate for patients in first remission as well as relapsed patients, there is still disagreement regarding OS and potential disadvantages due to toxicity and an increased rate of secondary malignancies (Colombat 2001; Forstpointner 2004; Lenz 2004; Lenz 2004a; Deconinck 2005; Hiddemann 2005; Marcus 2005; Hiddemann 2006; Sebban 2006; Van Oers 2006; Weigert 2006; Buske 2007; Herold 2007; Sacchi 2007).

How the intervention might work

Myeloablative doses of chemotherapy or irradiation permits the application of higher doses of anti-cancer therapy and provides potentially better tumour control. On the other hand, this therapy leads to various adverse events, including damage to the bone marrow and decreased production of leucocytes (white blood cells), thrombocytes (platelets) and erythrocytes (red blood cells). To restore the bone marrow's ability to produce blood cells, the patient receives stem cells from his own body, called autologous stem cell transplantation. These cells are mobilised and collected in advance, frozen and stored and returned to the patient after HDT.

Why it is important to do this review

At this stage, no systematic review or meta-analysis of ASCT in FL patients are available. Because of the uncertainties of HDT followed by ASCT mentioned above, we undertook this review. We aimed to obtain more evidence regarding the clinical benefit (OS, PFS) and the therapy-related risks (treatment related mortality (TRM), adverse events), by systematically analysing the reliability and validity of the data and by considering only RCTs for our review.

OBJECTIVES

To compare the effectiveness of HDT with ASCT to chemotherapy or immuno-chemotherapy in patients with newly diagnosed or relapsed FL.

METHODS

Criteria for considering studies for this review

Types of studies

Any published (including Internet publication) or unpublished RCTs (including cluster randomised trials) were eligible for inclusion in the review. We did not apply time or language restrictions.

Types of participants

Adult male and female patients (≥ 18 years of age) with a confirmed diagnosis of FL.

Types of interventions

The main intervention was HDT with ASCT compared with chemotherapy and immuno-chemotherapy. We considered any chemotherapeutic and immunochemotherapeutic regimen for comparison.

Types of outcome measures

Primary outcomes

- Overall survival (OS) was evaluated as the primary efficacy endpoint

Secondary outcomes

- Progression-free survival (PFS)
- Response rate (RR)
- Qualitiy of life (Qol)
- Treatment-related mortality (TRM)
- Adverse events
- Secondary malignancies

Search methods for identification of studies

Electronic searches

We adopted search strategies from those suggested in Chapter Six of the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011). To reduce language bias we did not apply language restriction.

The search covered major medical databases from 1985 to September 2011:

- the Cochrane Central Register of Controlled Trials (CENTRAL), see Appendix 1 and Appendix 2;
- MEDLINE, for search strategy see Appendix 3 and
- EMBASE, see Appendix 4.

We searched conference proceedings of annual meetings of the following societies not included in CENTRAL for abstracts:

- ASH (American Society of Hematology) 2007 to 2010
- ASCO (American Society of Clinical Oncology) 2007 to 2010
- EBMT (European Group for Bone and Marrow Transplantation) 2007 to 2010.

We searched the database of ongoing trials: Metaregister of controlled trials:

- www.controlled-trials.com/mrct/
- www.eortc.be/
- www.ctc.usyd.edu.au/
- www.trialscentral.org/index.html

Searching other resources

We handsearched references.

- References of all identified trials, relevant review articles and current treatment guidelines

Data collection and analysis

Selection of studies

Two review authors (MS, NS) screened the titles and abstracts of studies identified from the above sources. At the first screening, we discarded studies that were clearly ineligible. If this could not be done satisfactorily based on title and abstract, we obtained the full text version and discussed eligibility. The aim was to be overly inclusive rather than to risk losing relevant studies. We assessed selected studies using an eligibility form to determine whether they met the inclusion criteria; we resolved any disagreement by discussion. If necessary, we sought further information from the authors where articles contained insufficient data to make a decision about eligibility. The eligibility form contained the following questions.

1. Is the study described as randomised?
2. Is the diagnosis of FL histologically confirmed?
3. Were the participants in the experimental group treated by HDT and ASCT?
4. Were the participants in the control group treated by chemotherapy or immunochemotherapy?

Data extraction and management

Two review authors (MS, NS) independently extracted data concerning details of study population, intervention and outcomes using a standardised data extraction form. This form included the following terms.

- General information: author, title, source, publication date, country, language, duplicate publications.
- Quality assessments: sequence generation, allocation concealment, blinding (participants, personnel, outcome assessors), incomplete outcome data, selective outcome reporting, other sources of bias.
- Study characteristics: trial design, aims, setting and dates, source of participants, inclusion/exclusion criteria, treatment allocation, comparability of groups, subgroup analysis, statistical methods, power calculations, treatment cross-overs, compliance with assigned treatment, length of follow-up, time point of randomisation (upfront, after induction).
- Participant characteristics: age, gender, ethnicity, number of participants recruited / allocated / evaluated, participants lost to follow-up, additional diagnoses, percentage actually receiving transplant; prognostic factors
- Interventions: setting, type of (multi-agent) chemotherapy (intensity of induction and conditioning regimen, number of cycles, with or without radiation), stem cell source (bone marrow or peripheral blood); transplantation with or without growth factor support, transplant details, infection prophylaxis, type of maintenance treatment, type of salvage treatment.
- Outcomes: OS, PFS, relapse rate, TRM, adverse events, QoL.

Where possible, we sought missing data from the authors.

Assessment of risk of bias in included studies

Two review authors (MS, NS) evaluated independently all included trials using a list of selected quality criteria according to the recommendations in Chapter Eight of the *Cochrane Handbook for Systematic Reviews of Interventions* for the following criteria (Higgins 2011).

- Sequence generation.
- Allocation concealment.
- Blinding (participants, personnel, outcome assessors).
- Incomplete outcome data.
- Selective outcome reporting.
- Other sources of bias.

The review authors judged each criteria, based on a three-point scale ("Yes" (low risk of bias), "No" (high risk of bias), "Unclear") and a summary description. We resolved disagreement by consensus. The review authors were not blinded to names of authors, institutions, journals, or the outcomes of the trials.

Measures of treatment effect

For binary outcomes, we calculated risk ratios (RR) with 95% confidence intervals (CI) for each trial. We planned to calculate continuous outcomes as mean difference (MD), but no continuous data were included. For time-to-event outcomes we extracted the hazard ratio (HR) from published data according to Parmar 1998 and Tierney 2007.

Dealing with missing data

We planned to follow the general recommendations for dealing with missing data in Cochrane reviews (Higgins 2011b):

- Whenever possible, we contacted the original investigators to request missing data.
- We would have clearly stated the assumptions of any methods used to cope with missing data (e.g. imputation of missing data and accounting for the fact that these were imputed with uncertainty).

Assessment of heterogeneity

Because of the small number of studies in each analysis (two), the quantification of heterogeneity was not reliable. In meta-analyses with more trials, we would have assessed heterogeneity of treatment effects between trials using a Chi^2 test with a significance level at $P < 0.1$. In that case, we would have used the I^2 statistic to quantify possible heterogeneity ($I^2 > 30\%$ moderate heterogeneity, $I^2 > 75\%$ considerable heterogeneity) (Deeks 2011). We explored potential causes of heterogeneity by sensitivity and subgroup analyses where possible.

Assessment of reporting biases

We would have explored potential publication bias in meta-analyses with at least 10 trials by generating a funnel plot and statistically testing by means of a linear regression test. We would have considered a P value < 0.1 as significant for this test (Sterne 2011).

Data synthesis

We performed analyses according to the recommendations of chapter nine of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). We used aggregated data for analysis. For statistical analysis, we entered data into the Cochrane statistical package Review Manager 5 (Review Manager (RevMan)). One review author (MS) entered data into the software and a second review author (NS) checked it for accuracy. We performed meta-analyses using a random-effects model (for example, the generic inverse variance method for survival data outcomes and Mantel-Haenszel method for dichotomous data outcomes). We used the random-effects model in terms of sensitivity analyses.

Subgroup analysis and investigation of heterogeneity

We assessed heterogeneity of treatment effects between trials by using a CHI^2 test with a significance level at $P < 0.1$. The I^2 statistic was used to quantify possible heterogeneity. Wwe performed subgroup analyses on the following characteristics.

- Patients treated as front line, refractory or relapse with these treatments.

Subgroup analyses by age, sex or gender were not possible due to the limited amount of data available. Because of the same type of stem cell source in all trials, we did not perform subgroup analysis for this factor. Due to differences of type and intensity of preparative regimen in each trial, we also excluded subgroup analysis in this regard. Subgroup analysis of prognostic factors was left out because they were not reported in any one of the included trials.

Sensitivity analysis

- Quality components, including full text publications/abstracts, preliminary results versus mature results.
- Fixed-effect modelling versus random-effects modelling.

RESULTS

Description of studies

Results of the search

Our literature search produced 3046 potentially relevant references related to treatment of patients with FL. Of these, we excluded 2987 at the initial stage of screening because they did not fulfil our predefined inclusion criteria. The remaining 59 publications were retrieved as full text publications or abstract publications for detailed evaluation. Of these 59 publications, 40 were excluded and finally five trials (19 publications) with 1093 patients were formally included in the main analyses of this review. The overall number of trials screened, identified, selected, excluded and included was documented with reasons according to PRISMA flow diagram (see Figure 1) (Moher 2009).

Figure 1. PRISMA flow diagram

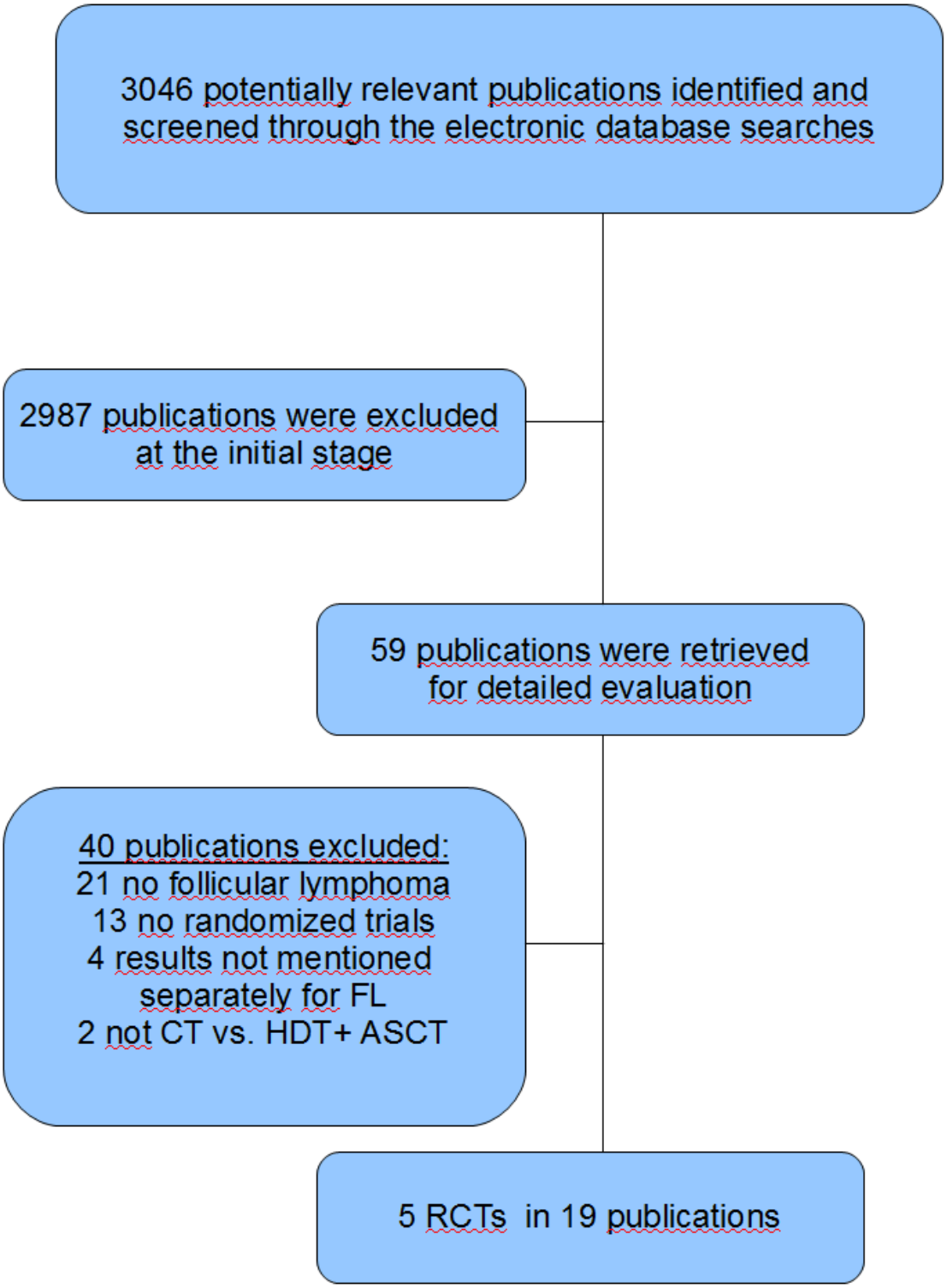


Figure 1. (Continued)

Included studies

The characteristics of included trials are also summarised in Characteristics of included studies.

We included five trials (CUP trial; GELA/GELF-94; GITMO/IIL; GLSG; GOELAMS 064) in the review; four trials in previously untreated patients (GELA/GELF-94; GITMO/IIL; GLSG; GOELAMS 064) and one trial in patients with relapsed FL (CUP trial). The earliest trial recruited in the time period between 1993 and 1997 and the latest between 2000 and 2005. We extracted the data from full text publications for all trials.

Design

Of the five included trials, four trials were two-armed RCTs and one trial was a three-armed RCT (CUP trial). The CUP trial randomised patients to chemotherapy only, unpurged stem cells and purged stem cells. We evaluated the two arms (purged and unpurged) together in this review. Of the five multi-centre trials, three were national (GITMO/IIL; GLSG; GOELAMS 064) and two were international (CUP trial; GELA/GELF-94). The control arm consisted in one trial of chemotherapy only (CUP trial) and in three trials of chemotherapy plus interferon (GELA/GELF-94; GLSG; GOELAMS 064). In one trial, the chemotherapy arm was supplemented by the monoclonal antibody rituximab (GITMO/IIL).

Sample size

The smallest trial (CUP trial) randomised 89 patients (70 analysed) and the largest trial 401 patients (GELA/GELF-94).

Location

The included trials came from a range of research groups from different countries. The trials were conducted in the following countries: one trial in Germany (GLSG); one trial in France and Belgium (GELA/GELF-94), one trial in different centres of European countries (CUP trial); one trial in France (GOELAMS 064) and one trial in Italy (GITMO/IIL).

Participants

A total of 1.105 male and female patients with histologically proven FL were randomised. For the majority of the patients, histopathologic diagnosis was made according to the Working-Formulation criteria of the National Cancer Institute and reviewed according to the REAL classification. One thousand and ninety-three of the randomised patients were evaluated.

Interventions

Patients from included trials were treated either with HDT + ASCT or chemotherapy/immunochemotherapy.

The HDT consisted of CHOP cyclophosphamide and total body irradiation (TBI) in the CUP trial; cyclophosphamide, high-dose doxorubicin, prednisone, and vincristine (VCAP), ifosamide, methotrexate, and VP-16 (IMVP-16) and TBI in the GOELAMS 064 trial; and dexamethasone, cBCNU, melphalan, etoposide, and cytarabine (Dexa-BEAM), cyclophosphamide and TBI in the GLSG trial. In the GELA/GELF-94 trial, the HDT arm included TBI, CHOP, cyclophosphamide and etoposide. TBI was not scheduled for the intervention arm of the GITMO/IIL trial. Patients randomised to this arm were treated with doxorubicin, vincristine, and prednisone (APO), Ara-C, cisplatin, and dexamethasone (DHAP), etoposide, cyclophosphamide, mitoxantrone, melphalan and rituximab.

The chemotherapy regimens of the control arms were as follows: cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in two trials (CUP trial; GITMO/IIL); cyclophosphamide, doxorubicin, teniposide, and prednisolone (CHVP) for two trials (GELA/GELF-94; GOELAMS 064); and mitoxantrone, chlorambucil, and prednisone (MCP) or CHOP in one trial (GLSG). In three trials, interferon α was given in addition to the therapy of the control-arm (GELA/GELF-94; GLSG; GOELAMS 064). In one trial (GITMO/IIL), the chemotherapy arm was supplemented by the monoclonal antibody rituximab. In one trial (CUP trial), the control arm included only chemotherapy.

In all five trials the type of stem cell source was the harvest of peripheral blood stem cells (PBSC).

Outcomes

Primary outcome measure

Overall survival was analysed in four trials (CUP trial; GELA/GELF-94; GITMO/IIL; GOELAMS 064). The median follow-up time for OS was as follows: 51 months for the GELA/GELF-94 trial; 69 months for the CUP trial; 108 months for the GOELAMS 064 trial and 51 months for the GITMO/IIL trial. In one trial, OSoverall-survival was not reported (GLSG).

Secondary outcome measures

Four trials reported PFS (CUP trial; GITMO/IIL; GLSG; GOELAMS 064). Response rate was analysed in three trials (GELA/GELF-94; GITMO/IIL; GOELAMS 064). Four trials mentioned treatment-related mortality and secondary malignancies (GELA/GELF-94; GITMO/IIL; GLSG; GOELAMS 064). Three trials evaluated adverse events (GITMO/IIL; GLSG; GOELAMS 064) and no trial mentioned quality of life.

Three trials additionally reported event-free survival (EFS) (GELA/GELF-94; GITMO/IIL;GOELAMS 064); this endpoint was not analysed in this systematic review. EFS was calculated as the time period form the random assignment to induction failure (stable disease at the end of treatment or progression during treatment), death

irrespective of the cause, progression after partial response (PR), relapse after complete response (CR), or last follow-up. Compared to that, PFS is defined from the end of successful induction therapy until documented progression or death and not directly estimable from EFS.

Funding

Roche supported in part the GITMO/IIL trial, providing rituximab for all the patients. The GOELAMS 064 trial was partly supported by grants from the French Ministry of Health (Paris, France) and Schering-Plough. Schering-Plough also supported the GELA/GELF-94 trial.

Conflict of interest

In one trial, the authors indicated no potential conflict of interest (CUP trial). In all other trials, conflict of interests was not mentioned.

Excluded studies

For information on excluded trials see Characteristics of excluded studies, where reasons for the exclusion are listed.

We excluded a total of 40 articles after detailed evaluation of full text publications. The main reasons for exclusion were:

- 13 articles: non-randomised comparisons or reviews;
- 2 articles: not CT versus HDT + ASCT;
- 21 articles: no patients with FL;
- 4 articles: no separated results reported for patients with FL and no reply from the authors for further details.

Risk of bias in included studies

Overall the quality of included trials is moderate. For more details see 'Risk of bias' tables of the included trials in the tables of Characteristics of included studies. The 'Risk of bias' graph illustrates the proportion of studies with each of the judgements "low risk", "high risk" or "unclear risk" of bias for each entry in the tool (see Figure 2). The 'Risk of bias' summary figure presents all of the judgements in a cross-tabulation of study by entry (see Figure 3).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

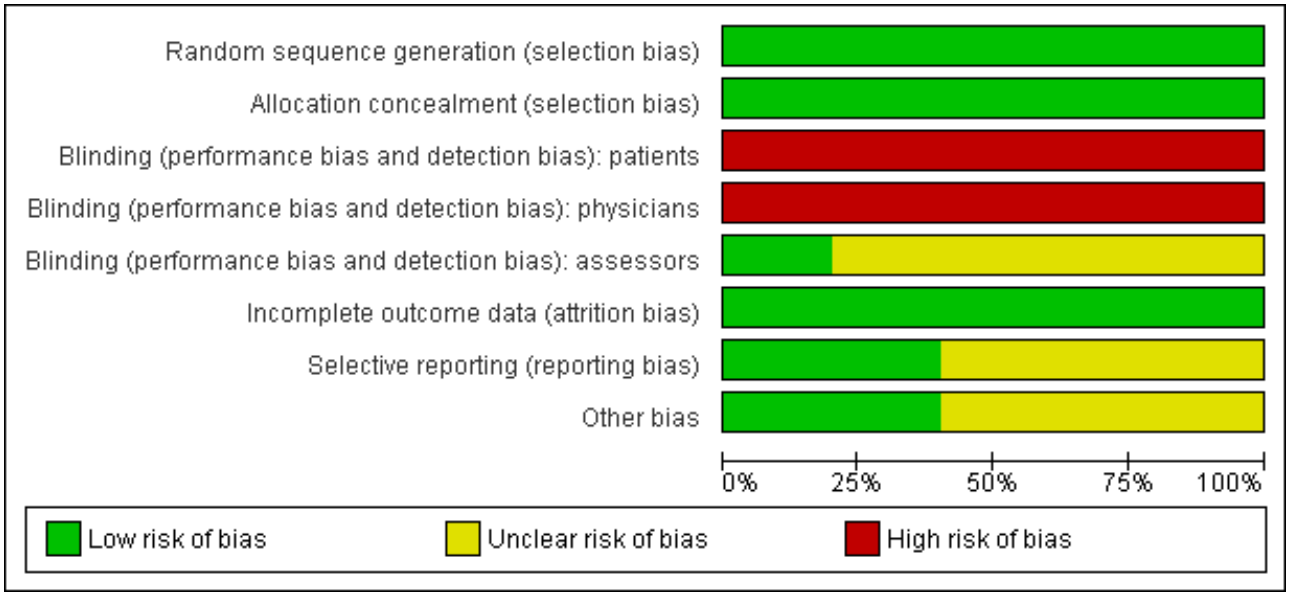
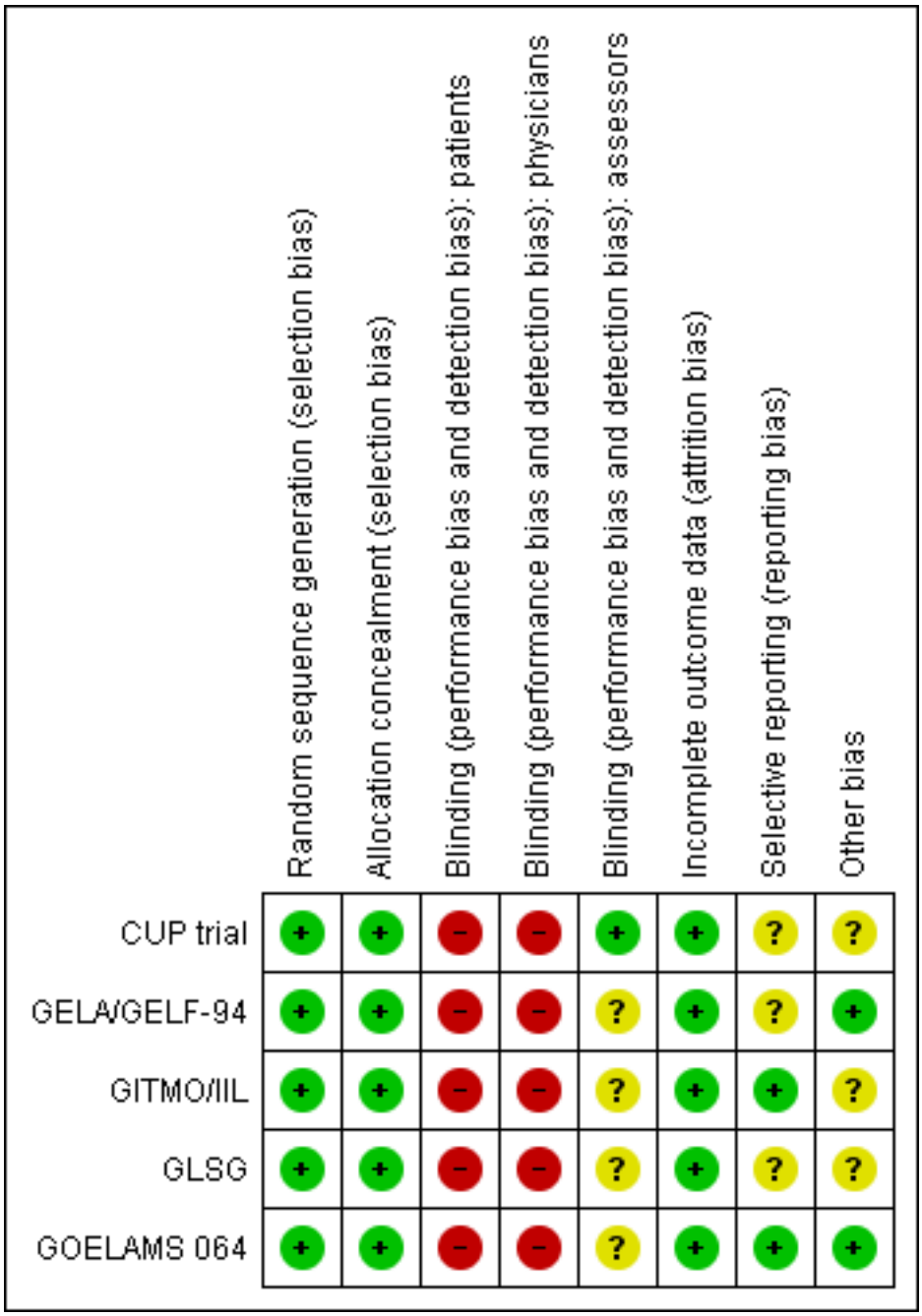


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Treatment allocation of patients was carried out centrally for all trials. In the GITMO/IIL trial, a centralised computer generated a simple randomisation sequence. In the GELA/GELF-94 trial, treatment allocation of patients was assigned by the study co-ordinating centre. In the CUP trial, random assignment using the method of minimization was performed at the Medical Research Council Clinical Trials Unit in London by telephone or fax.

In all included trials, sequence generation was judged to be adequate.

Blinding

No trial reported information about blinding of patients and physicians. We judged "high risk of bias" for the question of blinding of patients and physicians, because usually trials evaluating the effect of stem cell transplantation are not blinded, leading to a potential high risk of bias. We judged four of five trials as "unclear" for the question of blinding of the outcome assessors, as this topic was not reported (GELA/GELF-94; GITMO/IIL; GLSG; GOELAMS 064). One trial reported information about blinding of the outcome assessors and was judged as "low risk of bias" (CUP trial).

Incomplete outcome data

According to the intention-to-treat principle most trials (CUP trial; GELA/GELF-94; GITMO/IIL; GOELAMS 064) included all randomised patients in the analysis. In the GLSG trial, 55 of the 307 randomised patients were not analysed because they did not receive the assigned therapy. This question was judged as "low risk of bias" for all five included trials.

Selective reporting

Two study protocols for the five included trials were available (GITMO/IIL; GOELAMS 064). In both trials, the same outcomes as indicated in the study protocol were reported in the full text publications. Therefore we judged risk of these two trials as low.

Other potential sources of bias

In the CUP trial, the protocol was amended in March 1996 to enable centres that felt uncomfortable treating relapsed patients without HDT and ASCT to provide this regimen to all patients. After March 1996, patients were randomised to purged versus unpurged stem cells only.

The GITMO/IIL trial was stopped early after a planned interim analysis, indicating a significant EFS advantage in patients treated with HDT + ASCT and rituximab compared with CHOP and rituximab. The risk of bias for the premature closure is judged as "unclear".

In the GLSG trial, the risk of bias is judged as "unclear", due to the fact that in July 1998 all patients received CHOP instead of MCP or CHOP. This protocol amendment is based on the publication of a randomised comparison of CHOP with MCP showing that MCP was associated with a significant impairment of haematopoietic stem cell mobilisation.

A potential source of bias are uncertainties in the HR calculation. In three trials the HRs for OS (GELA/GELF-94; GITMO/IIL; GOELAMS 064) and in two for PFS (GITMO/IIL; GOELAMS 064) had to be based on the survival curves. In all cases, constant censoring was assumed as described by Tierney 2007.

Effects of interventions

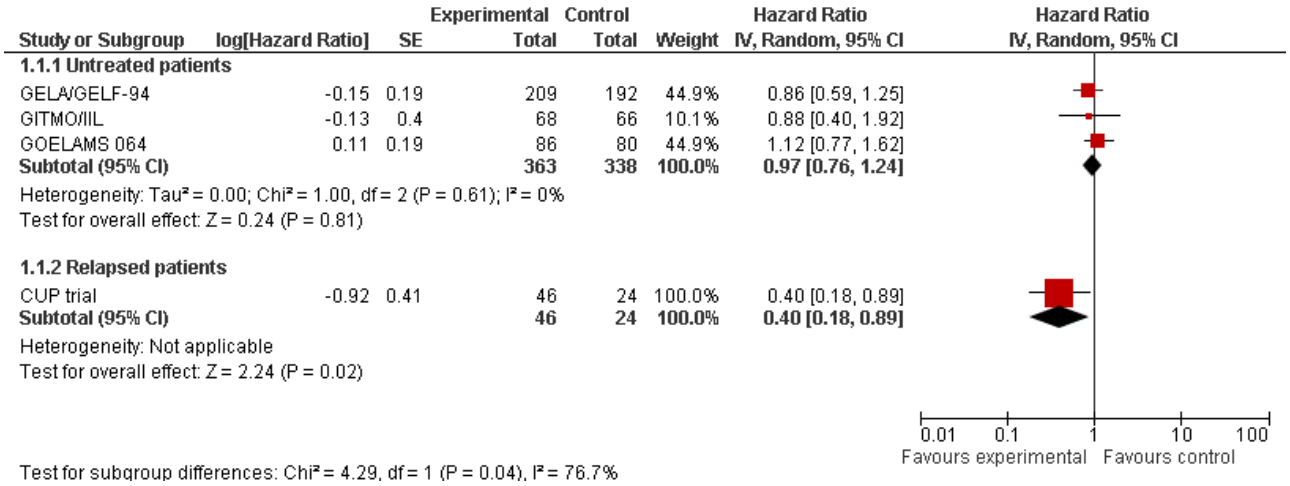
See: **Summary of findings for the main comparison**

Primary outcome: Overall survival (OS)

Except for the GLSG trial, all trials reported outcomes for OS (four trials, 771 patients).

The meta-analysis of trials evaluating previously untreated patients with FL included 701 patients in three trials. This analysis did not show a statistically significant difference between patients treated with HDT + ASCT compared with chemotherapy only (HR = 0.97; 95% confidence interval (CI) 0.76 to 1.24; P = 0.81) (Figure 4). The subgroup analysis for the rituximab-containing regimen confirms this finding (HR = 0.88; 95% CI 0.40 to 1.92; P = 0.75). However, only one trial was included in this analysis (GITMO/IIL) and the test for differences across subgroups for this analysis is not statistically significant (P = 0.88).

Figure 4. Forest plot of comparison: 1 Overall survival, outcome: 1.1 Stage of disease.



The trial evaluating relapsed patients, the CUP trial is the only trial with a statistically significant benefit for patients in the HDT + ASCT arm (HR = 0.40; 95% CI 0.18 to 0.89; P = 0.002). However, with only 70 patients, it is a small trial (Figure 4).

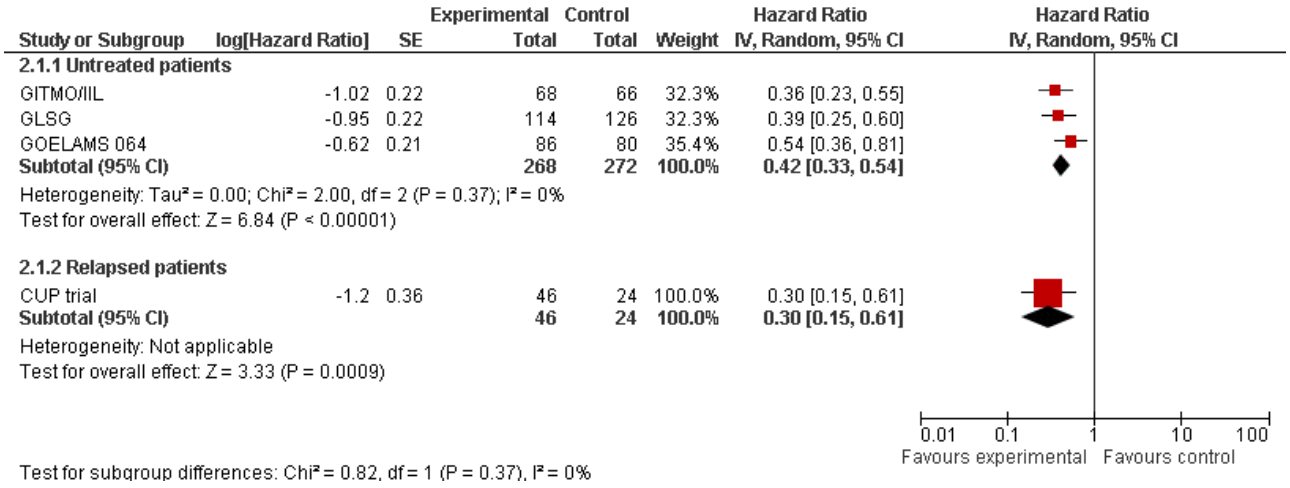
2.Secondary Outcomes

Progression-free survival (PFS)

Four trials with a total of 610 patients reported PFS (CUP trial; GITMO/IIL; GLSG; GOELAMS 064).

The meta-analysis in trials with previously untreated patients with FL showed statistically significant improved PFS (HR = 0.42; 95% CI 0.33 to 0.54; P < 0.00001) (three trials, N = 540) (GITMO/IIL; GLSG; GOELAMS 064) (Figure 5). The subgroup analysis for trials adding rituximab in both arms (one trial, GITMO/IIL) confirms this result (HR = 0.36; 95% CI 0.23 to 0.55; P < 0.00001). Again, there is no statistically significant interaction between subgroups, with or without rituximab (P = 0.53).

Figure 5. Forest plot of comparison: 2 Progression-free survival, outcome: 2.1 Stage of disease.



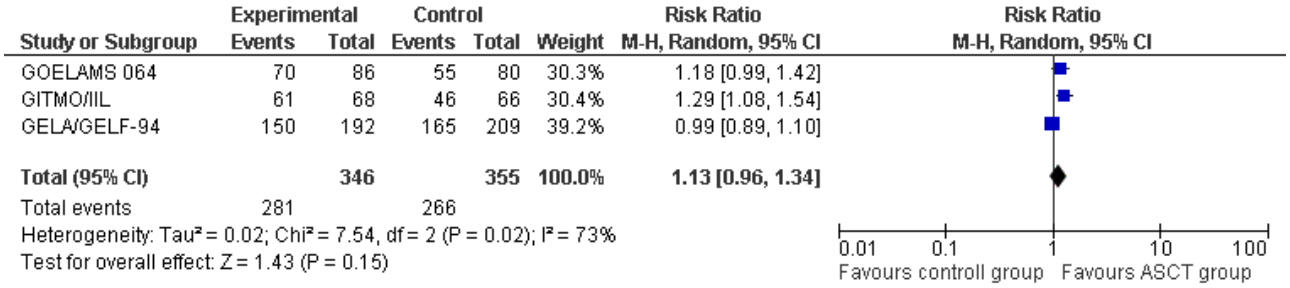
The analysis of the trial randomising patients with relapsed FL (N = 70) showed an statistically significant improvement of PFS (HR = 0.30 (95% CI 0.15 to 0.61; P = 0.0009) (CUP trial) (Figure 5).

Response Rate (RR)

Overall response rate (ORR)

The meta-analysis included a total of 701 patients from three trials, all in previously untreated patients (GELA/GELF-94; GITMO/IIL; GOELAMS 064). No evidence of a statistically significant difference between the HDT + ASCT group and the chemotherapy group was found (RR = 1.13; 95% CI 0.96 to 1.34). There is a hint for heterogeneity between trials visible in the forest plot (Figure 6).

Figure 6. Forest plot of comparison: 3 Overall response rate, outcome: 3.1 All trials (previously untreated patients).



The only trial (GITMO/IIL) adding rituximab in both arms showed a statistically significant advantage for the HDT + ASCT arm (RR = 1.29, 95% CI 1.08 to 1.54; P = 0.006), however, the test for differences between subgroups is not statistically significant (P = 0.14).

Complete response (CR)

Two trials with 535 patients reported CR (GELA/GELF-94; GITMO/IIL). No evidence for difference between both arms was found (RR: 1.11, 95% CI 0.64 to 1.92; P = 0.71).

A subgroup analysis was performed for the GITMO/IIL trial, evaluating additional rituximab in both arms. In this trial, CR was statistically significantly improved in the HDT + ASCT-arm (RR = 1.37, 95% CI, 1.11 to 1.70; P = 0.003), but the test for interaction between subgroups is not statistically significant (P = 0.06).

Treatment-related mortality (TRM)

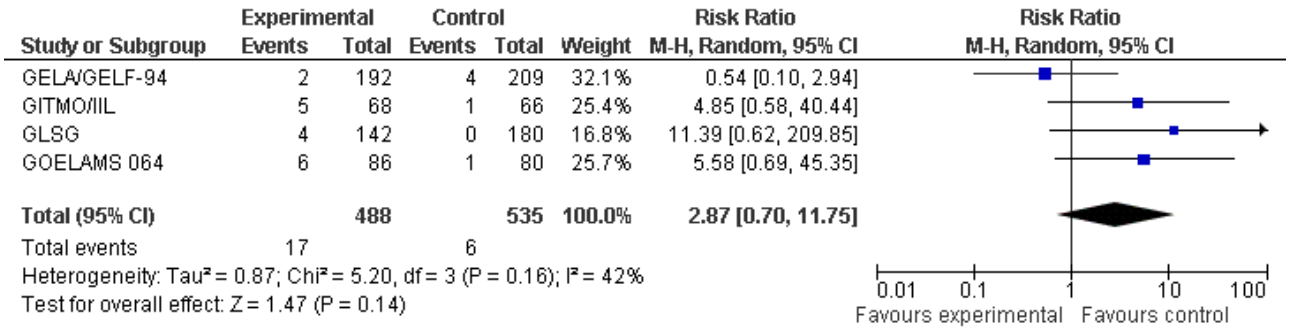
Four trials comprising 941 previously untreated patients reported data of TRM and were meta-analysed (GELA/GELF-94; GITMO/IIL; GLSG; GOELAMS 064). Treatment-related mortality was balanced for both arms and did not show statistically significant differences between both arms (RR = 1.28; 95% CI 0.25 to 6.61; P = 0.77). The same is true for the subgroup analysis including additional rituximab (RR = 1.46; 95% CI 0.25 to 8.44; P = 0.68) and no statistically significant difference across subgroups was found (P = 0.83). However, only one trial (GITMO/IIL) was included in the rituximab-subgroup.

Secondary malignancies (SM)

Four trials in previously untreated patients gave details on the development of secondary malignancies, AML (acute myeloid leukaemia) and MDS (myelodysplastic syndrome) as well as on the development of solid cancer (GELA/GELF-94; GITMO/IIL; GLSG; GOELAMS 064). The occurrence of MDS/AML was reported in four trials including 1023 patients. With a median follow-up time between 44 and 108 months, there is no statistically significant difference in development of MDS or AML for the compared two interventions (RR = 2.87, 95% CI 0.70, 11.75; P = 0.14), however, the

trend is in favour of the control arm consisting of chemotherapy only (Figure 7).

Figure 7. Forest plot of comparison: 4 Secondary Malignancies, outcome: 4.1 AML/MDS.



Three trials reported data to the development of solid cancers (GELA/GELF-94; GITMO/IIL; GOELAMS 064) with a follow-up time between 51 and 108 months. The meta-analysis did not show statistical significant differences between the two arms (RR= 1.20; 95% CI 0.25, 5.77; P = 0.82).

After a median follow-up time of 51 months, the two subgroup analyses with the trial including additional rituximab did not show statistical significant differences between the arms, neither for the occurrence for AML/MDS (RR = 4.85; 95% CI 0.58 to 40.44; P = 0.14) nor solid cancer (RR = 0.32; 95% CI 0.03 to 3.03; P = 0.32) (GITMO/IIL). Both test for differences across subgroups were not statistically significant (P = 0.67; P = 0.24).

Adverse Events

All adverse events reported in the trials are presented in Table 1.

Three trials reported on some adverse events (GITMO/IIL; GLSG; GOELAMS 064), two trials did not report on any adverse event (CUP trial; GELA/GELF-94). As expected, more adverse events were observed in the HDT + ASCT arm, especially haematological toxicities. The GLSG trial, in particular, shows a high rate of haematological toxicities such as anaemia, leucocytopenia, granulocytopenia and thrombocytopenia in the HDT + ASCT arm. All three trials describe the higher occurrence of non-haematological toxicities as well as acute infections in the HDT + ASCT arm.

Quality of life

None of the trials reported quality of life.

DISCUSSION

Summary of main results

The following findings emerge from this meta-analysis.

1. Based on currently available research results, HDT followed by ASCT does not lead to an overall survival advantage in comparison with chemotherapy or immuno-chemotherapy in patients with previously untreated FL. We found a statistically significant advantage for relapsed patients in the HDT + ASCT arm, but this was evaluated in one trial only.
2. High-dose therapy and ASCT shows a statistically significant improvement of PFS compared with the chemotherapy or immuno-chemotherapy, both in previously untreated patients as well as in relapsed patients. This huge effect also is seen in the trial adding rituximab in both treatment arms.
3. No statistically significant differences were shown between HDT + ASCT and the control intervention in terms of TRM, secondary AML/MDS or solid cancers, or overall or complete response rates. These outcomes were reported for previously untreated patients only.
4. Adverse events were observed more frequently in the HDT + ASCT arm. Again, these outcomes were reported for previously untreated patients only.
5. None of the trials reported quality of life.

One reason why the statistically significant PFS did not translate into an OS advantage could be the clinical course of FL. Patients with similar OS may nevertheless have differing lengths of time without symptoms, time to progression or requirement for treatment, depending both on initial treatment and disease characteristics. Follicular lymphoma is an indolent disease, often relapsing after successful first-line treatment in shorter intervals and requiring salvage therapy. These additional treatment approaches could influence the outcome OS more than the first-line treatment patients received. Especialy nowadays, in the era of rituximab, salvage therapy is becoming more effective. The influence of salvage therapy is visible in the GITMO/IIL trial: 70% of patients who relapsed after CHOP-R underwent salvage therapy with rituximab and HDT + ASCT, leading to a complete response rate of 85% and 81% OS at three years. Except for the GITMO/IIL trial, all the included studies started before rituximab was introduced, therefore, most patients will have received rituximab at the time of relapse.

There are no statistically significant differences in terms of secondary malignancies, especially the appearance of AML/MDS or solid cancers. None of the individual trials included in the meta-analysis described a statistically significant increase of either AML/MDS or solid cancers. Thus, secondary malignancies are probably not the reason for the missing OS benefit. However, long-term adverse effects such as secondary malignancies are important after HDT + ASCT and can occur later than the reported observation times of the discussed trials.

Overall completeness and applicability of evidence

Five trials, published in nineteen abstracts and full-texts, compared the use of HDT therapy followed by ASCT chemotherapy or immuno-chemotherapy for FL in adults. Because of the clinical homogeneity of the included trials, we pooled their outcomes in one meta-analysis. Apart from the exception of quality of life, which was not reported in any trial, the included trials reported our previously specified protocol outcomes. The randomised trials were heterogeneous in terms of usage of TBI in myeloablative regimen, chemotherapies, interferon and rituximab dosages. The low number of included studies made it difficult to explore the potential impact of these differences in subgroup analyses and to evaluate potential heterogeneity in detail.

Only one of the five trials evaluated the impact of HDT followed by ASCT in patients with relapsed FL. Although the results of this trial are statistically significant in terms of overall and progression-free survival, the small number of patients evaluated may have overestimated the effects.

Only three of the five included trials reported adverse events, with more haematological and non-haematological events in the group receiving HDT + ASCT. The non-publication of adverse events in two trials could have introduced bias.

Quality of life was not reported in any of the trials.

Two trials included patients with FL grade 3b (GITMO/IIL; GOELAMS 064), usually treated as aggressive lymphoma. The inclusion of these patients may have biased the results.

Quality of the evidence

The main analysis according to the inclusion criteria of our protocol included five RCTs with 1093 patients with FL. The overall quality of the five included trials was moderate. The trials were conducted between 1993 and 2005. All the included trials were reported as randomised and as open-label studies. None of the included trials reported allocation concealment. The open-label design and unclear allocation concealment could lead to selection, performance or detection biases. In terms of the treatment schedule, the protocol of two trials was amended, indicating a potential risk of reporting bias. In one trial, all patients having received CHOP instead of MCP or CHOP since July 1998. This protocol amendment is based on the publication of a randomised comparison of CHOP with MCP showing that MCP was associated with a significant impairment of haematopoietic stem cell mobilisation. The other protocol was amended in March 1996 to enable centres that felt uncomfortable treating relapsed patients without HDT + ASCT to provide this therapy to all patients. The premature closure of one trial after a planned interim analysis, indicating a significant EFS advantage in patients treated with HDT + ASCT therapy and rituximab compared with CHOP plus rituximab arm could have introduced bias.

A potential source of bias are uncertainties in the HR calculation. In three trials the HRs for OS and in two for PFS were calculated from survival curves with a constant censoring as described by Tierney 2007.

The studies included in this review offered a variety of chemotherapy regimens, such as CHOP, CHVP, APO, DHAP, MCP and VCAP. The low number of included studies made it difficult to explore these regimens in detail in subgroup analyses and to interpret potential underlying heterogeneity.

Potential biases in the review process

We tried to avoid bias by doing all relevant processes in duplicate. We are not aware of any obvious flaws in our review process.

Agreements and disagreements with other studies or reviews

To our knowledge, this comprehensive evaluation is the first meta-analysis focusing on patients with FL that compares HDT followed by ASCT with chemotherapy or immuno-chemotherapy.

Therapeutic options for treatment of patients with FL have been investigated in three other Cochrane reviews (Vidal 2009; Schulz 2007; Baldo 2010). The review of Baldo et al. (Baldo 2010) determined the effects of interferon (IFN) in the maintenance therapy of FL. With a total of 1563 patients in eight trials, the review showed that addition of IFN as maintenance therapy for FL improves PFS in contrast to OS. Seven randomised controlled trials involving 1943 patients with FL, mantle cell lymphoma, or other indolent lymphomas were meta-analysed in the systematic review of Schulz et al. (Schulz 2007), comparing chemotherapy plus rituximab with chemotherapy alone. Schulz could demonstrate that rituximab given in addition to chemotherapy, statistically significantly improves overall survival, overall response rate, complete response rate, and disease control compared with chemotherapy alone. On the subject of maintenance treatment with rituximab in FL patients, Vidal et al. (Vidal 2009) published a Cochrane review with comparable results. The review includes five trials with 1056 adult FL patients. The analysis of OS included 895 patients in four trials. Patients treated with rituximab as maintenance therapy had a significantly better OS compared with observation alone (HR = 0.53; 95% CI 0.38 to 0.73).

Greb et al. (Greb 2011) investigated the benefit of HDT with ASCT in first-line treatment for patients with aggressive NHL. The meta-analysis included 15 randomised controlled trials with 3079 patients and showed that despite higher CR rates, there is no benefit for HDT with ASCT as a first-linr treatment in patients with aggressive NHL. Thus this review has results in line with our analysis.

AUTHORS' CONCLUSIONS

Implications for practice

There is currently no evidence that HDT followed by ASCT improves OS in newly diagnosed patients with FL. However, the increase of PFS is statistically significant and led to a huge effect favouring the HDT + ASCT arm, even in the trial adding rituximab in both intervention arms. We demonstrated no statistically significant differences in terms of treatment related mortality, secondary AML/MDS or solid cancers, however, acute adverse events are observed more frequently in the HDT + ASCT arm, especially haematological toxicities and infections. None of the trials evaluated quality of life.

For patients with relapsed FL, there is evidence (one trial, N = 70) that the addition of HDT followed by ASCT is advantageous regarding overall survival and progression-free survival.

Implications for research

Randomised controlled trials with longer follow-up periods and rituximab-containing chemotherapy in both arms are needed to determine the potential effect of HDT in the era of rituximab and to evaluate whether the seen PFS-benefit will translate into a survival advantage.

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REFERENCES

References to studies included in this review

CUP trial *{published data only}*

Schouten HC, Kvaloy S, Sydes M, Qian W, Fayers PM. The CUP trial: a randomized study analyzing the efficacy of high dose therapy and purging in low-grade non-Hodgkin's lymphoma (NHL). *Annals of Oncology* 2000;**11 Suppl 1**:91-4.

* Schouten HC, Qian W, Kvaloy S, Porcellini A, Hagberg H, Johnson HE, et al. High-dose therapy improves progression-free survival and survival in relapsed follicular non-Hodgkin's lymphoma: results from the randomized European CUP trial. *Journal of Clinical Oncology : The American Society of Clinical Oncology* 2003;**21**(21):3918-27.

Stade BG, Koll R, Drexler K, Spaethe R, Gibson D, Schouten H. European cup: a randomised trial comparing the efficacy of chemotherapy versus purged or unpurged autologous bone marrow transplantation (ABMT) in patients with relapsed follicular non-hodgkin's lymphoma (NHL). *Onkologie* 1994;**17**(Suppl 2):143.

GELA/GELF-94 *{published data only}*

Sebban C, Brice P, Delarue R, Haioun C, Souleau B, Mounier N, et al. Impact of rituximab and/or high-dose therapy with autotransplant at time of relapse in patients with follicular lymphoma: a GELA study. *Journal of Clinical Oncology* 2008;**26**(21):3614-20.

* Sebban C, Mounier N, Brousse N, Belanger C, Brice P, Haioun C, et al. Standard chemotherapy with interferon compared with CHOP followed by high-dose therapy with autologous stem cell transplantation in untreated patients with advanced follicular lymphoma: the GELF-94 randomized study from the Groupe d'Etude des Lymphomes de l'Adulte (GELA). *Blood* 2006;**108**(8):2540-4.

Sebban C, et al. A randomized trial in follicular lymphoma comparing a standard chemotherapy regimen with 4 courses of CHOP followed by autologous stem cell transplant with TBI: the GELF94 trial from GELA. European Hematology Association Website http://www.ehaweb.org. 2003.

Sebban C, et al. Comparison of CHVP + interferon with CHOP followed by autologous stem cell transplantation with TBI conditioning regimen in untreated patients with high tumor burden follicular lymphoma: a result of the randomized GELF94 trial (G.E.L.A. Study Group). *Blood* 2003;**102.11 Pt 1**:104a.

GITMO/IIL *{published data only}*

Ladetto M, Corradini P, Vallet S, Benedetti F, Vitolo U, Martelli M, et al. High rate of clinical and molecular remissions in follicular lymphoma patients receiving high-dose sequential chemotherapy and autografting at diagnosis: a multicenter, prospective study by the Gruppo Italiano Trapianto Midollo Osseo (GITMO). *Blood* 2002;**100**(5):1559-65.

* Ladetto M, De Marco F, Benedetti F, Vitolo U, Patti C, Rambaldi A, et al. Prospective, multicenter randomized GITMO/IIL trial comparing intensive (R-HDS) versus conventional (CHOP-R) chemoimmunotherapy in high-risk follicular lymphoma at diagnosis: the superior disease control of R-HDS does not translate into an overall survival advantage. *Blood* 2008;**111**(8):4004-13.

Ladetto M, Ricca I, Benedetti F, Liberati M, Vitolo U, Musso M, et al. Multicenter prospective randomized GITMO trial comparing high dose sequential chemotherapy with autografting and CHOP both supplemented with rituximab in poor-risk follicular lymphoma: early evaluation on treatment feasibility and response rate [abstract]. *Bone Marrow Transplantation* 2003;**31**(Suppl 1):7-8.

Ladetto M, Vallet S, Benedetti F, Vitolo U, Martelli M, Callea V, et al. Prolonged survival and low incidence of late toxic sequelae in advanced follicular lymphoma treated with a TBI-free autografting program: updated results of the multicenter consecutive GITMO trial. *Leukemia* 2006;**20**(10):1840-7.

GLSG *{published data only}*

Lenz G, Dreyling M, Schiegnitz E, Forstpointner R, Wandt H, Freund M, et al. Myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission prolongs progression-free survival in follicular lymphoma: results of a prospective, randomized trial of the German Low-Grade Lymphoma Study Group. *Blood* 2004;**104**(9):2667-74.

Lenz G, Dreyling M, Schiegnitz E, Haferlach T, Hasford J, Unterhalt M, et al. Moderate increase of secondary hematologic malignancies after myeloablative radiochemotherapy and autologous stem-cell transplantation in patients with indolent lymphoma: results of a prospective randomized trial of the German Low Grade Lymphoma Study Group. Journal of Clinical Oncology 2004; Vol. 22, issue 24:4926-33.

* Nickenig C, Dreyling M, Hoster E, Ludwig WD, Dorken B, Freund M, et al. Initial chemotherapy with mitoxantrone, chlorambucil, prednisone impairs the collection of stem cells in patients with indolent lymphomas-results of a randomized comparison by the German Low-Grade Lymphoma Study Group. *Annals of Oncology* 2007;**18**(1):136-42.

Nickenig C, Dreyling M, Hoster E, Pfreundschuh M, Trumper L, Reiser M, et al. Combined cyclophosphamide, vincristine, doxorubicin, and prednisone (CHOP) improves response rates but not survival and has lower hematologic toxicity compared with combined mitoxantrone, chlorambucil, and prednisone (MCP) in follicular and mantle cell lymphomas: results of a prospective randomized trial of the German Low-Grade Lymphoma Study Group. *Cancer* 2006;**107**(5):1014-22.

GOELAMS 064 *{published data only}*

Deconinck E, Colombat P, Foussard C, Milpied N. High dose therapy with autologous purged stem cell transplantation and doxorubicin based immunochemotherapy in patients with advanced follicular lymphoma: A GOELAMS study [Abstract]. *Annals of Oncology* 2005;**16 Suppl 5**(12):109.

Deconinck E, Foussard C, Bertrand P, et al. Value of autologous stem cell transplantation in first line therapy of follicular lymphoma with high tumor burden: final results of the randomized GOELAMS 064 trial. *Blood* 2003;**102.11 Pt 1**:246a.

Deconinck E, Foussard C, Milpied N, Bertrand P, Michenet P, Cornillet-LeFebvre P, et al. High-dose therapy followed by autologous purged stem-cell transplantation and doxorubicin-based chemotherapy in patients with advanced follicular lymphoma: a randomized multicenter study by GOELAMS. *Blood* 2005;**105**(10):3817-23.

* Gyan E, Foussard C, Bertrand P, Michenet P, Le Gouill S, Berthou C, et al. High-dose therapy followed by autologous purged stem cell transplantation and doxorubicin-based chemotherapy in patients with advanced follicular lymphoma: a randomized multicenter study by the GOELAMS with final results after a median follow-up of 9 years. *Blood* 2009;**113**(5):995-1001.

References to studies excluded from this review

Baldissera 2006 *{published data only}*

Baldissera RC, Nucci M, Vigorito AC, Maiolino A, Simoes BP, Lorand-Metze I, et al. Frontline therapy with early intensification and autologous stem cell transplantation versus conventional chemotherapy in unselected high-risk, aggressive non-Hodgkin's lymphoma patients: a prospective randomized GEMOH report. *Acta Haematologica* 2006;**115**(1-2):15-21.

Brice 2000 *{published data only}*

Brice P, Simon D, Bouabdallah R, Belanger C, Haioun C, Thieblemont C, et al. High-dose therapy with autologous stem-cell transplantation (ASCT) after first progression prolonged survival of follicular lymphoma patients included in the prospective GELF 86 protocol. *Annals of Oncology* 2000;**11**(12):1585-90.

Cao 2001 *{published data only}*

Cao TM, Horning S, Negrin RS, Hu WW, Johnston LJ, Taylor TL, et al. High-dose therapy and autologous hematopoietic-cell transplantation for follicular lymphoma beyond first remission: the Stanford University experience. *Biology of Blood & Marrow Transplantation* 2001;**7**(5):294-301.

De Souza 2003 *{published data only}*

De Souza C, Cardoso RB, Simoes BP, Maiolino A, Moraes AA, Ruiz MA. Prospective randomized study comparing the third generation VACOP-B regimens versus 6 week VACOP-B Plus high-dose sequential followed by autologous bone marrow transplantation in unselected high-risk IPI non Hodgkin's lymphoma. A GEMOH report. *Blood* 2003;**102**(11 Pt 2):268b.

De Souza 2004 *{published data only}*

De Souza CA, Cardoso RB, Simoes BP, Maiolino A, Moraes AJ, Ruiz MA, et al. Prospective randomised study comparing 12-week VACOP-B regimen versus 6-week VACOP-B plus high-dose sequential followed by autologous bone marrow transplantation in high-risk IPI aggressive non-Hodgkin lymphoma: a Brazilian GEMOH report [abstract]. *Bone Marrow Transplantation* 2004;**33**(Suppl 1):349.

Gianni 1997 *{published data only}*

Gianni AM, Bregni M, Siena S, Brambilla C, Di Nicola M, Lombardi F, et al. High-dose chemotherapy and autologous bone marrow transplantation compared with MACOP-B in aggressive B-cell lymphoma.[see comment]. *New England Journal of Medicine* 1997;**336**(18):1290-7.

Guglielmi 1993 *{published data only}*

Guglielmi C, Chauvin F, Hagenbeek A, Somers R, Van der LJ, Coiffier B, et al. The PARMA International randomized prospective study in relapsed non-Hodgkin's lymphoma: second interim analysis of 172 patients and update (as of 20/11/92: 200 patients) [abstract]. 5th International Conference on Malignant Lymphoma, Lugano, Switzerland, June. 1993.

Hagenbeek 1991 *{published data only}*

Hagenbeek A, Philip T, Bron D, Guglielmi C, Coiffier B, Gisselbrecht C, et al. The Parma international randomized study in relapsed non Hodgkin lymphoma: 1st interim analysis of 128 patients (as 15 January 1991: 153 patients). *Bone Marrow Transplantation* 1991;**7 Suppl 2**:142.

Haioun 1993 *{published data only}*

Haioun C, Lepage E, Gisselbrecht C, Coiffier B, Bosly A, Tilly H, et al. Autologous bone marrow transplantation (ABMT) versus sequential chemotherapy in first complete remission aggressive non-Hodgkin's lymphoma (NHL): a study on 469 patients (LNH87 protocol) [abstract]. 5th International Conference on Malignant Lymphoma, Lugano, Switzerland, June. 1993.

Haioun 1994 *{published data only}*

Haioun C, Lepage E, Gisselbrecht C, Coiffier B, Bosly A, Tilly H, et al. Comparison of autologous bone marrow transplantation with sequential chemotherapy for intermediate-grade and high-grade non-Hodgkin's lymphoma in first complete remission: a study of 464 patients. Groupe d'Etude des Lymphomes de l'Adulte.[see comment]. *Journal of Clinical Oncology* 1994;**12**(12):2543-51.

Haioun 1997 *{published data only}*

Haioun C, Lepage E, Gisselbrecht C, Bastion Y, Coiffier B, Brice P, et al. Benefit of autologous bone marrow transplantation over sequential chemotherapy in poor-risk aggressive non-Hodgkin's lymphoma: updated results of the prospective study LNH87-2. Groupe d'Etude des Lymphomes de l'Adulte. *Journal of Clinical Oncology* 1997;**15**(3):1131-7.

Intragumtornchai 2000 *{published data only}*

Intragumtornchai T, Prayoonwiwat W, Numbenjapon T, Assawametha N, O'Charoen R, Swasdikul D. CHOP versus CHOP plus ESHAP and high-dose therapy with autologous peripheral blood progenitor cell transplantation for high-intermediate-risk and high-risk aggressive non-Hodgkin's lymphoma. *Clinical Lymphoma* 2000;**1**(3):219-25.

Intragumtornchai 2006 *{published data only}*

Intragumtornchai T, Bunworasate U, Nakorn TN, Rojnuckarin P. Rituximab-CHOP-ESHAP vs CHOP-ESHAP-high-dose therapy vs conventional CHOP chemotherapy in high-intermediate and high-risk aggressive non-Hodgkin's lymphoma. *Leukemia & Lymphoma* 2006;**47**(7):1306-14.

Kaiser 2002 *{published data only}*

Kaiser U, Uebelacker I, Abel U, Birkmann J, Trumper L, Schmalenberg H, et al. Randomized study to evaluate the

use of high-dose therapy as part of primary treatment for "aggressive" lymphoma.[see comment]. *Journal of Clinical Oncology* 2002;**20**(22):4413-9.

Kluin-Nelemans 2001 *{published data only}*

Kluin-Nelemans HC, Zagonel V, Anastasopoulou A, Bron D, Roozendaal KJ, Noordijk EM, et al. Standard chemotherapy with or without high-dose chemotherapy for aggressive non-Hodgkin's lymphoma: randomized phase III EORTC study. [see comment]. *Journal of the National Cancer Institute* 2001;**93**(1):22-30.

Leppa 2006 *{published data only}*

Leppa S, Linna M, Nyman H, Taimela E. Cost-effectiveness of rituximab maintenance treatment versus autologous stem cell transplantation (ASCT) in patients with relapsed follicular lymphoma (FL). Blood. 2006; Vol. 108, issue 11.

Marin 2001 *{published data only}*

Marin GH, Menna ME, Bergna MI, Malacalza J, Martin C, Mendez MC, et al. Induction of anti-tumor activity following autologous stem cell transplantation: immunotherapeutic implications. *Transplantation Proceedings* 2001;**33**(1-2):2004-7.

Martelli 1996 *{published data only}*

Martelli M, Vignetti M, Zinzani PL, Gherlinzoni F, Meloni G, Fiacchini M, et al. High-dose chemotherapy followed by autologous bone marrow transplantation versus dexamethasone, cisplatin, and cytarabine in aggressive non-Hodgkin's lymphoma with partial response to front-line chemotherapy: a prospective randomized italian multicenter study. *Journal of Clinical Oncology* 1996;**14**(2):534-42.

Martelli 1999 *{published data only}*

Martelli M, Gherlinzoni F, Zinzani PL, Meloni G, Cantonetti M, Storti S. Early autologous stem cell transplantation as first-line therapy in poor prognosis non Hodgkin's lymphoma (NHL): An Italian randomized trial. *Annals of Oncology* 1999;**10**(Suppl 3):78.

Martelli 2003 *{published data only}*

Martelli M, Gherlinzoni F, De Renzo A, Zinzani PL, de Vivo A, Cantonetti M, et al. Early autologous stem-cell transplantation versus conventional chemotherapy as front-line therapy in high-risk, aggressive non-Hodgkin's lymphoma: an Italian multicenter randomized trial. *Journal of Clinical Oncology* 2003;**21**(7):1255-62.

Martinez 1995 *{published data only}*

Martinez C, Mateu R, Sureda A, Brunet S, Amill B, Madoz P, et al. Peripheral blood stem cell mobilization following salvage chemotherapy (IAPVP-16) plus granulocyte colony-stimulating factor and autografting for non-Hodgkin's lymphoma. *Transplantation Proceedings* 1995;**27**(4):2355-6.

McBride 1996 *{published data only}*

McBride JA, Pugh WC. Autologous bone marrow transplantation in relapsed non-Hodgkin's lymphoma.[comment]. *New England Journal of Medicine* 1996;**334**(15):991-2.

Metzner 2002 *{published data only}*

Metzner B. High-dose therapy and autologous bone marrow transplantation for follicular lymphoma in first remission. *Strahlentherapie und Onkologie* 2002;**178**(6):353, 2002.

Moser 2005 *{published data only}*

Moser EC, Noordijk EM, Carde P, Tirelli U, Baars JW, Thomas J, et al. Late non-neoplastic events in patients with aggressive non-Hodgkin's lymphoma in four randomized European Organisation for Research and Treatment of Cancer trials. *Clinical Lymphoma & Myeloma* 2005;**6**(2):122-30.

Mounier 2000 *{published data only}*

Mounier N, Haioun C, Cole BF, Gisselbrecht C, Sebban C, Morel P, et al. Quality of life-adjusted survival analysis of high-dose therapy with autologous bone marrow transplantation versus sequential chemotherapy for patients with aggressive lymphoma in first complete remission. Groupe d'Etude les Lymphomes de l'Adulte (GELA). *Blood* 2000;**95**(12):3687-92.

Olivieri 2005 *{published data only}*

Olivieri A, Santini G, Patti C, Chisesi T, De Souza C, Rubagotti A, et al. Upfront high-dose sequential therapy (HDS) versus VACOP-B with or without HDS in aggressive non-Hodgkin's lymphoma: long-term results by the NHLCSG. *Annals of Oncology* 2005;**16**(12):1941-8.

Pettengell 1996 *{published data only}*

Pettengell R, Radford JA, Morgenstern GR, Scarffe JH, Harris M, Woll PJ, et al. Survival benefit from high-dose therapy with autologous blood progenitor-cell transplantation in poor-prognosis non-Hodgkin's lymphoma. *Journal of Clinical Oncology* 1996;**14**(2):586-92.

Philip 1991 *{published data only}*

Philip T, Chauvin F, Bron D, Guglielmi C, Hagenbeek A, Coiffier B, et al. PARMA international protocol: pilot study on 50 patients and preliminary analysis of the ongoing randomized study (62 patients). *Annals of Oncology* 1991;**2 Suppl 1**:57-64.

Philip 1995 *{published data only}*

Philip T, Guglielmi C, Hagenbeek A, Somers R, Van der Lelie H, Bron D, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. [see comment]. *New England Journal of Medicine* 1995;**333**(23):1540-5.

Philip 1995a *{published data only}*

Philip T, Guglielmi C, Chauvin F, Hagenbeek A, Van der Lely J, Bron D, et al. Autologous bone marrow transplantation (ABMT) vs conventional chemotherapy (DHAP) in relapsed non-Hodgkin's lymphoma (NHL): final analysis of the Parma randomized study (216 patients) [abstract]. *Journal of Clinical Oncology* 1995;**14**:390.

Proctor 2003 *{published data only}*

Proctor SJ. Phase III Randomized Study of High-Dose Chemotherapy and Radiotherapy Plus Autologous Bone Marrow Transplantation in Patients With Aggressive Non-Hodgkin's

Lymphoma. National Institutes of Health, ClinicalTrials Gov [http://www.clinicaltrials.gov]. 2003.

Rabinowe 1990 *{published data only}*

Rabinowe S, Freedman A, Demetri G, Soiffer R, Ritz J, Blake K. Randomized double blinded trial of rh-GM-CSF in patients with B-cell non-Hodgkin's lymphoma (B-NHL) undergoing high dose chemoradiotherapy and monoclonal antibody purged autologous bone marrow transplantation (ABMT). *Blood* 1990;**76**(10 Suppl 1):161a.

Rohatiner 1991 *{published data only}*

Rohatiner AZ, Price CG, Arnott S, Norton A, Evans ML, Cotter F, et al. Myeloablative therapy with autologous bone marrow transplantation as consolidation of remission in patients with follicular lymphoma. *Annals of Oncology* 1991;**2 Suppl 2**:147-50.

Rohatiner 1994 *{published data only}*

Rohatiner AZ, Johnson PW, Price CG, Arnott SJ, Amess JA, Norton AJ, et al. Myeloablative therapy with autologous bone marrow transplantation as consolidation therapy for recurrent follicular lymphoma. *Journal of Clinical Oncology* 1994;**12**(6):1177-84.

Rohatiner 1994a *{published data only}*

Rohatiner AZ, Freedman A, Nadler L, Lim J, Lister TA. Myeloablative therapy with autologous bone marrow transplantation as consolidation therapy for follicular lymphoma. *Annals of Oncology* 1994;**5 Suppl 2**:143-6.

Santini 1991 *{published data only}*

Santini G, Coser P, Chisesi T, Porcellini A, Sertoli R, Contu A, et al. Autologous bone marrow transplantation for advanced stage adult lymphoblastic lymphoma in first complete remission. Report of the Non-Hodgkin's Lymphoma Cooperative Study Group (NHLCSG). *Annals of Oncology* 1991;**2 Suppl 2**:181-5.

Santini 1997 *{published data only}*

Santini G, Salvagno L. VACOP-B vs VACOP-B + autologous BM transplantation (ABMT) for aggressive non-Hodgkin's lymphoma. A study of the Non-Hodgkin's Lymphoma Cooperative Study Group (NHLCSG) [abstract]. *Bone Marrow Transplant* 1997;**19 Suppl**:S154.

Santini 1998 *{published data only}*

Santini G, Salvagno L, Leoni P, Chisesi T, De Souza C, Sertoli MR, et al. VACOP-B versus VACOP-B plus autologous bone marrow transplantation for advanced diffuse non-Hodgkin's lymphoma: results of a prospective randomized trial by the non-Hodgkin's Lymphoma Cooperative Study Group. *Journal of Clinical Oncology* 1998;**16**(8):2796-802.

Sonnen 1998 *{published data only}*

Sonnen R, Schmitz N, Dreger P, Lietz B, Kuse R. High dose chemotherapy followed by autologous stem cell-transplantation in B-high-grade non-hodgkin's lymphoma patients with unfavourable risk factors; a pilot study. *Annals of Hematology* 1998;**77 Suppl 2**:S65.

Sweetenham 2001 *{published data only}*

Sweetenham JW, Santini G, Qian W, Guelfi M, Schmitz N, Simnett S, et al. High-dose therapy and autologous stem-cell transplantation versus conventional-dose consolidation/maintenance therapy as postremission therapy for adult patients with lymphoblastic lymphoma: Results of a randomized trial of the european group for blood and marrow transplantation and the united kingdom lymphoma group. *Journal of Clinical Oncology* 2001;**19**(11):2927-36.

Winter 2005 *{published data only}*

Winter JN. The role of high-dose therapy followed by autologous purged stem cell transplantation in previously untreated patients with advanced follicular lymphoma. *Current Hematology Reports* 2005;**4**(4):249-51.

Additional references

Anderson 1998

Anderson JR, Armitage JO, Weisenburger DD. Epidemiology of the non-Hodgkin's lymphomas: distributions of the major subtypes differ by geographic locations. Non-Hodgkin's Lymphoma Classification Project. *Annals of Oncology* 1998;**9**(7):717-20.

Andreadis 2005

Andreadis C, Schuster SJ, Chong EA, Svoboda J, Luger SM, Porter DL, et al. Long-term event-free survivors after high-dose therapy and autologous stem-cell transplantation for low-grade follicular lymphoma. *Bone Marrow Transplantation* 2005;**36**(11):955-61.

Ardeshna 2003

Ardeshna KM, Smith P, Norton A, Hancock BW, Hoskin PJ, MacLennan KA, et al. Long-term effect of a watch and wait policy versus immediate systemic treatment for asymptomatic advanced-stage non-Hodgkin lymphoma: a randomised controlled trial. *Lancet* 2003;**362**(9383):516-22.

Armitage 1998

Armitage JO, Weisenburger DD. New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. Non-Hodgkin's Lymphoma Classification Project. *Journal of Clinical Oncology* 1998;**16**(8):2780-95.

Baldo 2010

Baldo P, Rupolo M, Compagnoni A, Lazzarini R, Bearz A, Cannizzaro R, et al. Interferon-alpha for maintenance of follicular lymphoma. *Cochrane Database of Systematic Reviews* 20 January 2010, Issue 1:CD004629. [DOI: 10.1002/14651858.CD004629]

Brandt 2001

Brandt L, Kimby E, Nygren P, Glimelius B. A systematic overview of chemotherapy effects in indolent non-Hodgkin's lymphoma. *Acta Oncologica* 2001;**40**(2-3):213-23.

Brown 2009

Brown JR, Freedman AS. ASCT in follicular lymphoma. Nature reviews. Clinical Oncology 2009; Vol. 6, issue 7:380-2.

Buske 2005

Buske C, Dreyling M, Unterhalt M, Hiddemann W. Transplantation strategies for patients with follicular lymphoma. *Current Opinion Hematology* 2005;**12**(4):266-72.

Buske 2007

Buske C, Unterhalt M, Hiddeman W. Therapy of follicular lymphoma [Therapie des follikularen Lymphoms.]. *Internist (Berl)* 2007;**48**(4):372-81.

Clarke 2002

Clarke CA, Glaser SL. Changing incidence of non-Hodgkin lymphomas in the United States. *Cancer* 2002;**94**(7):2015-23.

Colombat 2001

Colombat P, Salles G, Brousse N, Eftekhari P, Soubeyran P, Delwail V, et al. Rituximab (anti-CD20 monoclonal antibody) as single first-line therapy for patients with follicular lymphoma with a low tumor burden: clinical and molecular evaluation. *Blood* 2001;**97**(1):101-6.

Deconinck 2005

Deconinck E, Foussard C, Milpied N, Bertrand P, Michenet P, Cornillet-LeFebvre P, et al. High-dose therapy followed by autologous purged stem-cell transplantation and doxorubicin-based chemotherapy in patients with advanced follicular lymphoma: a randomized multicenter study by GOELAMS. *Blood* 2005;**105**(10):3817-23.

Deeks 2011

Deeks JJ, Higgins JPT, Altman DG. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011 Available from www.cochrane-handbook.org.

Diaz-Alderete 2008

Diaz-Alderete A, Doval A, Camacho F, Verde L, Sabin P, Arranz-Saez R, et al. Frequency of BCL2 and BCL6 translocations in follicular lymphoma: relation with histological and clinical features. *Leukemia & Lymphoma* 2008;**49**(1):95-101.

Egger 1997

Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**(7109):629-34.

Fisher 2004

Fisher SG, Fisher RI. The epidemiology of non-Hodgkin's lymphoma. *Oncogene* 2004;**23**(38):6524-34.

Forstpointner 2004

Forstpointner R, Dreyling M, Repp R, Hermann S, Hanel A, Metzner B, et al. The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared with FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. *Blood* 2004;**104**(10):3064-71.

Foster 2009

Foster M, Gabriel DA, Shea T. Role of hematopoietic stem cell transplant in the management of follicular lymphoma. *The Oncologist* 2009;**14**(7):726-38.

Gallagher 1986

Gallagher CJ, Gregory WM, Jones AE, Stansfeld AG, Richards MA, Dhaliwal HS, et al. Follicular lymphoma: prognostic factors for response and survival. *Journal of Clinical Oncology* 1986;**4**(10):1470-80.

Greb 2011

Greb A, Bohlius J, Schiefer D, Schwarzer G, Schulz H, Engert A. High-dose chemotherapy with autologous stem cell transplantation in the first line treatment of aggressive non-Hodgkin lymphoma (NHL) in adults. *Cochrane Database of Systematic Reviews* 2011;**4**:CD004024.

Groves 2000

Groves FD, Linet MS, Travis LB, Devesa SS. Cancer surveillance series: non-Hodgkin's lymphoma incidence by histologic subtype in the United States from 1978 through 1995. *Journal of the National Cancer Institute* 2000;**92**(15):1240-51.

Harris 1999

Harris NL, Jaffe ES, Diebold J, Flandrin G, Muller-Hermelink HK, Vardiman J, et al. The World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues. Report of the Clinical Advisory Committee meeting, Airlie House, Virginia, November, 1997. *Annals of Oncology* 1999;**10**(12):1419-32.

Herold 2007

Herold M, Haas A, Srock S, Neser S, Al-Ali KH, Neubauer A, et al. Rituximab added to first-line mitoxantrone, chlorambucil, and prednisolone chemotherapy followed by interferon maintenance prolongs survival in patients with advanced follicular lymphoma: an East German Study Group Hematology and Oncology Study. *Journal of Clinical Oncology* 2007;**25**(15):1986-92.

Hiddemann 2005

Hiddemann W, Kneba M, Dreyling M, Schmitz N, Lengfelder E, Schmits R, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. *Blood* 2005;**106**(12):3725-32.

Hiddemann 2006

Hiddemann W, Unterhalt M. Current treatment strategies in follicular lymphomas. *Annals of Oncology* 2006;**17 Suppl 10**:x155-9.

Higgins 2011

Higgins JPT, Altman DG. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version

5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Higgins 2011a

Higgins JPT, Deeks JJ. Chapter 7: Selecting studies and collecting data. In: Higgins JPT, Green S editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Higgins 2011b

Higgins JPT, Deeks JJ, Altman DG. Chapter 16: Special topics in statistics. In: Higgins JPT, Green S editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Horning 1984

Horning SJ, Rosenberg SA. The natural history of initially untreated low-grade non-Hodgkin's lymphomas. *New England Journal of Medicine* 1984;**311**(23):1471-5.

Horning 2000

Horning SJ. Follicular lymphoma: have we made any progress?. *Annals of Oncology* 2000;**11 Suppl 1**:23-7.

Jemal 2005

Jemal A, Murray T, Ward E, Samuels A, Tiwari RC, Ghafoor A, et al. Cancer statistics, 2005. *CA: A Cancer Journal for Clinicians* 2005;**55**(1):10-30.

Khouri 2008

Khouri IF, McLaughlin P, Saliba RM, Hosing C, Korbling M, Lee MS, et al. Eight-year experience with allogeneic stem cell transplantation for relapsed follicular lymphoma after nonmyeloablative conditioning with fludarabine, cyclophosphamide, and rituximab. *Blood* 2008;**111**(12):5530-6.

Korsmeyer 1992

Korsmeyer SJ. Bcl-2 initiates a new category of oncogenes: regulators of cell death. *Blood* 1992;**80**(4):879-86.

Lau 2006

Lau J, Ioannidis JP, Terrin N, Schmid CH, Olkin I. The case of the misleading funnel plot. *BMJ* 2006;**333**(7568):597-600.

Lefebvre 2011

Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011.

Lenz 2004

Lenz G, Dreyling M, Schiegnitz E, Forstpointner R, Wandt H, Freund M, et al. Myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission prolongs progression-free survival in follicular lymphoma: results of a prospective, randomized trial of the German Low-Grade Lymphoma Study Group. *Blood* 2004;**104**(9):2667-74.

Lenz 2004a

Lenz G, Dreyling M, Schiegnitz E, Haferlach T, Hasford J, Unterhalt M, et al. Moderate increase of secondary hematologic malignancies after myeloablative radiochemotherapy and autologous stem-cell transplantation in patients with indolent lymphoma: results of a prospective randomized trial of the German Low Grade Lymphoma Study Group. Journal of Clinical Oncology 2004; Vol. 22, issue 24:4926-33.

Marcus 2005

Marcus R, Imrie K, Belch A, Cunningham D, Flores E, Catalano J, et al. CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. *Blood* 2005;**105**(4):1417-23.

Moher 1999

Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. *Lancet* 1999;**354**(9193):1896-900.

Moher 2009

Moher D, Liberati A, Tetzlaff J, Altman DG, The Prisma Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Journal of Clinical Epidemiology* 2009;**62**(10):1006-12.

Muller 2005

Muller AM, Ihorst G, Mertelsmann R, Engelhardt M. Epidemiology of non-Hodgkin's lymphoma (NHL): trends, geographic distribution, and etiology. *Annals of Hematology* 2005;**84**(1):1-12.

Oliansky 2010

Oliansky DM, Gordon LI, King J, Laport G, Leonard JP, McLaughlin P, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of follicular lymphoma: an evidence-based review. *Biology of blood and marrow transplantation : American Society for Blood and Marrow Transplantation* 2010;**16**(4):443-68.

Ott 2002

Ott G, Katzenberger T, Lohr A, Kindelberger S, Rudiger T, Wilhelm M, et al. Cytomorphologic, immunohistochemical, and cytogenetic profiles of follicular lymphoma: 2 types of follicular lymphoma grade 3. *Blood* 2002;**99**(10):3806-12.

Parmar 1998

Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics in Medicine* 1998;**17**(24):2815-34.

Reiser 2002

Reiser M, Diehl V. Current treatment of follicular non-Hodgkin's lymphoma. *European Journal of Cancer* 2002;**38**(9):1167-72.

Review Manager (RevMan) [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008.

Rohatiner 2005

Rohatiner AZ, Gregory WM, Peterson B, Borden E, Solal-Celigny P, Hagenbeek A, et al. Meta-analysis to evaluate the role of interferon in follicular lymphoma. *Journal of Clinical Oncology* 2005;**23**(10):2215-23.

Sacchi 2007

Sacchi S, Pozzi S, Marcheselli L, Bari A, Luminari S, Angrilli F, et al. Introduction of rituximab in front-line and salvage therapies has improved outcome of advanced-stage follicular lymphoma patients. *Cancer* 2007;**109**(10):2077-82.

Schulz 2007

Schulz H, Bohlius J, Skoetz N, Trelle S, Kober T, Reiser M, et al. Chemotherapy plus Rituximab versus chemotherapy alone for B-cell non-Hodgkin's lymphoma. *Cochrane Database of Systematic Reviews* 2007;**CD003805**(4):CD003805.

Sebban 2006

Sebban C, Mounier N, Brousse N, Belanger C, Brice P, Haioun C, et al. Standard chemotherapy with interferon compared with CHOP followed by high-dose therapy with autologous stem cell transplantation in untreated patients with advanced follicular lymphoma: the GELF-94 randomized study from the Groupe d'Etude des Lymphomes de l'Adulte (GELA). *Blood* 2006;**108**(8):2540-4.

Sterne 2011

Sterne JAC, Egger M, Moher D. Chapter 10: Addressing reporting biases. In: Higgins JPT, Green S editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Symmans 1995

Symmans WF, Katz RL, Ordonez NG, Dalton H, Romaguera JE, Cabanillas F. Transformation of follicular lymphoma. Expression of p53 and bcl-2 oncoprotein, apoptosis and cell proliferation. *Acta Cytologica* 1995;**39**(4):673-82.

Tierney 2007

Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007;**8**:16.

Van Oers 2006

Van Oers MH, Klasa R, Marcus RE, Wolf M, Kimby E, Gascoyne RD, et al. Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-Hodgkin lymphoma in patients both with and without rituximab during induction: results of a prospective randomized phase 3 intergroup trial. *Blood* 2006;**108**(10):3295-301.

Vidal 2009

Vidal L, Gafter-Gvili A, Leibovici L, Shpilberg O. Rituximab as maintenance therapy for patients with follicular lymphoma. *Cochrane Database of Systematic Reviews* 2009;**Issue 2**:Art. No.: CD006552. DOI: 10.1002/14651858.CD006552.

Weigert 2006

Weigert O, Dreyling M, Unterhalt M, Hiddemann W, Buske C. Investigational strategies in autologous stem cell transplantation for follicular lymphoma. *Current Oncology Reports* 2006;**8**(5):368-75.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

CUP trial

Methods	• Randomised controlled trial with three arms: chemotherapy arm, unpurged HDT + ASCT arm and purged HDT + ASCT arm. • Conducted by the Univerity Hospital Maastricht, 140 patients from 36 centres in 11 countries in Europe and Australia were registered. • Recruitment period from August 1993 to April 1997. • 89 patients were randomly assigned. • 70 patients were randomised 1:1:1; 24 patients in chemotherapy arm; 22 patients in unpurged HDT + ASCT arm and 24 patients in purged HDT + ASCT arm. The remaining 19 patients were randomly assigned with a 1:1 ratio between HDT with or without purging only, because the protocol was amended in March 1996 to enable centres that felt uncomfortable treating relapsed patients without HDT and transplantation. • 51 patients not evaluated due to death (4), persistent marrow infiltration (4), refusal (6), no response or progressive disease (28), CNS involvement (2), histologic pathology (2) and unknown reasons (5). • Baseline patient characteristics described. • Median follow-up time: 69 months.
Participants	• Inclusion criteria: Patients with relapsed or progressive follicular NHL, aged between 15 and 65 years, with a WHO performance status of 0, 1 or 2.

CUP trial *(Continued)*

	• Exclusion criteria: Patients were excluded if they had previous radiotherapy (precluding TBI) or bone marrow harvest, CNS localisation; cumulative doxorubicin dose of more than 300 mg/m^2; prior malignancies with the exception of those originating in the skin (non-melanoma) or cervical carcinoma stage 1; cardiopulmonary, neurological, liver (liver enzymes more than 3x the upper limit of normal) or renal / creatinine > 150 µmol/L) dysfunction; evidence of histologically proven transformation; or HIV positivity. • No. of relapses: in purged HDT + ASCT arm 57% (1 relapse), 38% (2 relapses), 5% (3 relapses); in unpurged HDT + ASCT arm 75% (1 relapse), 20% (2 relapses), 5% (other); in chemotherapy arm 76% (1 relapse), 19% (2 relapses), 5% (3 relapses. • Mean age (range): chemotherapy arm: 47 (30 to 64) years; unpurged HDT + ASCT arm: 47 (30 to 60) years; purged HDT + ASCT arm: 48 (32 to 63). • Gender: chemotherapy arm: 12 males (50%), 12 females; unpurged HDT + ASCT arm: 15 males (68%), 7 females; purged HDT arm + ASCT: 10 males (42%), 14 females. • Similar baseline patients' characteristics in comparison arms. • Initial investigations: physical examination, WBC and differential, biochemistry, urine analysis, ECG, chest x-ray, computer tomography scan of the chest and abdomen, bone marrow histology and immunophenotyping, and peripheral blood cytology and immunophenotyping.

Interventions	• Induction therapy: Following registration, all patients were treated with three cycles of chemotherapy. CHOP chemotherapy (3-week cycle; cyclophosphamide 750 mg/m^2 IV, doxorubicin 50mg/m^2 IV and vincristine 1.4 mg/m^2 IV. on day 1; prednisone 100mg orally on days 1 to 5 was the recommended regimen, but any other suitable regimen was acceptable. Patients who achieved a CR or PR to induction therapy, had a WHO performance status of 0 to 2, had limited bone marrow infiltration (< 20%) and gave informed consent were eligible for random assignment .
	• Intervention after randomisation:
	  ◦ Chemotherapy arm: These patients had 3 additional cycles of chemotherapy;
	  ◦ Unpurged and purged HDT + ASCT arm: Within 4 weeks after harvesting, the patients had to be treated with cyclophosphamide 60 mg/kg on 2 days, in combination with fractionated or unfractionated TBI. Cryopreserved stem cells were thawed and infused by the IV route within 20 to 40 minutes.
	• Supportive treatment: With regard to post-chemotherapy treatment with radiotherapy, areas of prior bulky disease (> 5 cm) as assessed at time of entry in the trial, and/or areas that still showed residual masses 2 months after transplantation or after the completion of the chemotherapy could be irradiated, if this was considered feasible.

Outcomes	• Primary end point: PFS • Secondary end point: OS
Notes	Data included for the patients randomly assigned between the three planned arms, before protocol amendment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised controlled phase III trial
Allocation concealment (selection bias)	Low risk	"Random assignment, using the method of minimization, was performed at the MRC CTU in London by telephone or fax"
Blinding (performance bias and detection bias) patients	High risk	Usually trials evaluating stem cell transplantation are not blinded
Blinding (performance bias and detection bias)	High risk	Usually trials evaluating stem cell transplantation are not blinded

CUP trial *(Continued)*

physicians		
Blinding (performance bias and detection bias) assessors	Low risk	Assessors: "during the trial the investigators were blinded to the results". This is judged not to be a source of bias for OS and PFS
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Unclear risk	The protocol was amended in March 1996 to enable centres, that felt uncomfortable treating relapsed patients without HDT and transplantation.

GELA/GELF-94

Methods	• Randomised controlled trial with two arms: chemotherapy arm and HDT + ASCT arm. • Conducted by the Groupe d`Etude des Lymphomes de L`Adulte (GELA), 402 patients from 71 centres in France and Belgium were enrolled. • Recruitment period from July 1994 to March 2001. • 402 patients were enrolled, 401 patients were included in the final analysis and randomised 1:1, 209 in the CHVP-I arm and 192 in the CHOP-HDT arm; one patient was found to have a benign disease on revision and was rapidly withdrawn from the study.Staging: The extent of the disease was determined by a standardised evaluation including computed tomography of the chest, abdomen, and pelvis; bone marrow biopsy; bone marrow aspiration with complete blood counts; LDH level; and 2-microglobulin assay. PS was graded with the ECOG scale. A panel of 5 haemato-pathologists conducted a central pathology review. • Baseline patient characteristics described. • Median follow-up time: 51 months. • ITT analysis.
Participants	• Inclusion criteria: Patients had to be younger than 61years with untreated FL at bulky stage II disease or stage III or IV and require therapy because of high tumour burden. High tumour burden was defined by at least one of the following parameters using GELF criteria: systemic symptoms (> 10% weight loss, temperature > 38°C for more than 5 days, abundant night sweats); PS greater than 1 according to the ECOG scale; elevated LDH level; ß2-microglobulin level greater than 25.5 nM/L (3 µg/mL); a single lymph node larger than 7 cm; marked splenomegaly; organ failure; pleural effusion or ascites; orbital or epidural involvement; blood infiltration or cytopenia. • Exclusion criteria: Previous treatment for lymphoma; diagnosis more than 3 months before; blood creatinine level above 150 µM; history of another cancer except in situ breast cancer or uterine cancer; contraindication to doxorubicin, interferon or intensive therapy; positive serologic test for the HIV; or histologic transformation into a more aggressive lymphoma • Mean age: chemotherapy arm: 49 years; HDT + ASCT arm: 49 years. • Gender: chemotherapy arm: 114 males (55%), 95 females; HDT + ASCT: 107 males (56%), 85 females. • Disease Stage, No. (%): CT-arm: stage II 16 (8), stage III 26 (13), stage IV 160 (79); HDT + ASCT arm: stage II 11 (6), stage III 23 (12), stage IV 153 (82); Data were missing for 12 patients • FLIPI score, No.(%): chemotherapy arm: low risk 63 (32), intermediate risk 67 (34), high risk 69 (34); HDT + ASCT arm: low risk 55 (30), intermediate risk 79 (43), high risk 51 (27); data were missing for 17 patients. • Similar baseline patients' characteristics in comparison arms.
Interventions	• Conventional chemotherapy arm:

GELA/GELF-94 *(Continued)*

- Patients received 6-monthly courses of CHVP, with cyclophosphamide 600 mg/m^2, doxorubicin 25 mg/m^2, and teniposide 60 mg/m^2 on day 1 and prednisolone 40 mg/m^2 on days 1 to 5. Interferon alpha was given s.c. at a dosage of 5 Mio units (MU) 3 times a week. Patients then achieving a CR or PR received 6 courses of CHVP plus interferon every 2 months for 1 year. In the event of haematologic toxicity, the next chemotherapy cycle was postponed for 1 week and the dose of interferon was decreased to 3 MU. In the event of chronic grade 3 or 4 interferon-related toxicity, the dose of interferon was reduced to 3 MU. If grade 4 toxicity occurred despite this decreased dosage, interferon was stopped and chemotherapy was continued as scheduled.

- HDT + ASCT arm:
  - 4 cycles of CHOP every 3 weeks, with cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, and vincristine 1.4 mg/m^2 (max. 2mg) on day 1 and prednisolone 40mg/m^2 on days 1 to 5. Two weeks after the 4th course of CHOP, the response was assessed and patients with stable or progressive disease were considered to be non-responders and were treated according to the individual centre's policy. Responding patients (CR or PR) received a single course of cyclophosphamide 4500 mg/m^2, etoposide 450 mg/m^2 in 3 infusions, and G-CSF 300 µg from days 4 to 12 followed by PBSC harvest. PBSCs were harvested until 4x10^8 mononuclear cells/kg were obtained. HDT was instated 4 weeks later and compromised cyclophosphamide 60 mg/kg/d, mesna 60mg/kg/d, and etoposide 150mg/m^2 from day -6 to -5. Split TBI was then performed delivering 10 Gy in 5 fractions from day -3 to -1 followed by PBSC reinfusion on day 0. A change in the dose or a delay between 2 courses of CHOP was not recommended except in the case of grade 3 or 4 haematologic toxicity.
- Important treatment information: As the marketing of teniposide was stopped during this study, it was replaced by etoposide 100mg/m^2 on day 1.

Outcomes	• Primary objective: EFS • Secondary objectives: OS, RR, secondary malignancies, PFS
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomised study"
Allocation concealment (selection bias)	Low risk	"After stratification according to Center, eligible patients were assigned by the study coordinating Center"
Blinding (performance bias and detection bias) patients	High risk	Usually trials evaluating stem cell transplantation are not blinded
Blinding (performance bias and detection bias) physicians	High risk	Usually trials evaluating stem cell transplantation are not blinded
Blinding (performance bias and detection bias) assessors	Unclear risk	No information about blinding of the assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	According to the ITT principle
Selective reporting (reporting bias)	Unclear risk	For primary outcome, event-free survival was chosen. It is unclear why event-free survival was chosen and not overall survival. No protocol is available.

GELA/GELF-94 *(Continued)*

Other bias	Low risk	no indication for other sources of bias

GITMO/IIL

Methods	• Randomised controlled trial with two arms: chemotherapy arm and HDT + ASCT arm. • Conducted by the Gruppo Italiano Trapianto di Midollo Osseo (GITMO), Intergruppo Italiano Linfomi (IIL), 136 patients from 30 centres in Italy were enrolled. • Recruitment period from March 2000 to May 2005. • 136 Patients were randomised 1:1; 68 to control arm and 68 to HDT-arm. • 134 Patients were evaluated; 66 patients in the CHOP-arm and 68 patients in the HDT-arm. Two CHOP-Patients were not included in the analysis; One patient withdrew consent before treatment start and one patient lacked a documented aaIPI score of 2 or greater. • Baseline patient characteristics described. • Median follow-up time: 51 months. • ITT analysis
Participants	• Inclusion criteria: Patients aged 18 to 60 were eligible if they had Ann Arbor stage III or IV FL, according to REAL/WHO lymphoma classification (grades 1, 2, and 3, patients with grade 3b were not excluded). Eligible patients had no history of cancer and were chemotherapy-or extended field radiotherapy-free. Absence of concurrent heart, kidney, lung, or liver disease was required plus HIV and hepatitis C negativity. HBV positive patients without active viral replication were eligible under lamivudine prophylaxis. • Exclusion criteria: not reported • aaIPI 2 or more, No. (%): CHOP-arm: 61 (92); HDT + ASCT-arm: 59 (87) • FLIPI 3 or more, No. (%): CHOP-arm: 34 (51); HDT + ASCT-arm: 44 (65) • Mean age (range): CHOP-arm: 51 (22 to 59) years; HDT + ASCT-arm: 51 (25 to 59). • Gender: CHOP-arm: 40 males (61%), 26 females; HDT + ASCT-arm: 38 males (56%), 30 females. • Similar baseline patients' characteristics in comparison arms.

Interventions	• Conventional chemotherapy arm:
	  ◦ 6 courses of CHOP (cyclophosphamide/ doxorubicin/ vincristine, prednisone) supplemented by an identical number of rituximab courses (4 x 375 mg/m^2)
	• HDT+ ASCT arm:
	  ◦ *Phase 1 (intensive debulking):* 2 complete, full-dose APO (doxorubicin, vincristine, prednisone) courses, totaling four 75 mg/m^2 doxorubicin administrations. Patients not achieving CR received 2 additional DHAP (Ara-C, cisplatin, dexamethasone) courses.
	  ◦ *Phase 2 (High-dose chemotherapy)*: HD phase consisted of 2g/m^2 etoposide (VP16) followed by a chemotherapy-free interval of 40 days for optimal PBSC mobilization. During this phase, patients received 2 rituximab courses (375mg/m^2). Then, 7g/m^2 cyclophosphamide (Cy) was delivered. In vivo purging was performed by delivering 2 rituximab doses (375mg/m^2) on the day after Cy, and on the first day the pat had a white blood cell count greater than 1000/µL. HD courses were supported with G-CSF (5µg/kg/day). A minimum of 5 x 10^6 CD34+ cells/kg was required for autologous transplantation with PBSCs only (plus at least 3 x 10^6 CD34+ cells/kg or a bone marrow harvest as backup). Patients failing to meet this minimum did not undergo autografting.
	  ◦ *Phase 3* (*autografting*): The autografting conditioning regimen consisted of mitoxantrone (60 mg/m^2) on day -5 and melphalan (180 mg/m^2) on day -2.
	  ◦ Duration of treatment (days, cycles): A single APO-course consisted of doxorubicin (75 mg/m^2) on days 1 and 22, vincristine (1.2mg/m^2) on days 1 and 15, and prednisolone (50 mg/m^2) on days 1 and 22. The DHAP course consisted of cisplatin (100 mg/m^2) on day 1, Ara-C (4 g/m^2) on day 2, and dexamethasone (40 mg) on days 1 to 4.
	• Radiotherapy: Radiotherapy (30 to 36 Gy) was planned in both treatment arms on bulky sites or on residual masses approximately 2 months after the end of treatment.
	• Important treatment information:

GITMO/IIL *(Continued)*

	○ CHOP-arm in case of CHOP-R failure, most centres (90%) agreed to treat patients with R-HDS (cross-over). Only patients with the following characteristics were not considered eligible for cross-over: (1) localized, limited relapse, (2) relapses requiring a specific treatment such as CNS or testis, (3) the presence of severe co-morbidities, (4) age older than 60 years at the time of starting R-HDS and (5) patient refusal. Patients with histologic shifts at relapse were not excluded from cross-over and were included in analysis. When delivered at relapse, the R-HDS schedule was identical with the exception that no APO courses were delivered in order to avoid excessive cardiac toxicity in patients already treated with CHOP. Thus, these patients started their R-HDS schedule from 2 DHAP courses. ○ HDT-arm: in case of R-HDS failure, the salvage treatment was free. • Supportive treatment: In both treatment arms, patients in PR or who remained PCR received 2 final rituximab courses at the end of the program.
Outcomes	• Primary endpoint: EFS • Secondary endpoints: OS, RR, PFS, DFS, molecular outcome
Notes	• Supported in part by Roche

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Prospective multi-centre randomised trial
Allocation concealment (selection bias)	Low risk	"A centralized computer generated a simple randomisation sequence."
Blinding (performance bias and detection bias) patients	High risk	Usually trials evaluating stem cell transplantation are not blinded
Blinding (performance bias and detection bias) physicians	High risk	Usually trials evaluating stem cell transplantation are not blinded
Blinding (performance bias and detection bias) assessors	Unclear risk	No information about blinding of the assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT basis
Selective reporting (reporting bias)	Low risk	Protocol available at www.controlled-trials.com/mrct/trial/printfriendly/399237
Other bias	Unclear risk	Trial stopped early "A sample size of 246 patients (123 per arm) over 5 years was required to detect a 20% absolute increase (from 35% to 55%) in 3-year EFS with an error of .05 and a error of .20, with a median follow-up of 3 years. A single interim analysis was planned, including the 120 patients who completed the treatment before March 24, 2005. R-HDS showed a significant EFS improvement (29% absolute increase) compared to CHOP-R. This result led the steering committee to stop enrolment on May 30."

GLSG

Methods	• Randomised controlled trial with two arms: chemotherapy arm and HDT + ASCT arm.
	• Conducted by the German Low-Grade Lymphoma Study Group (GLGSG), 332 FL patients from 130 centres in Germany were enrolled.
	• Recruitment period from July 1996 to September 2000.
	• 332 were enrolled, 25 patients were not randomised (13 refused IFN α, 8 refused HDT + ASCT, 4 aged over 60); 307 Patients were randomised 1:1; 154 to IFN arm and 153 to HDT + ASCT arm
	• 240 Patients were evaluated; 126 patients in the IFN-arm and 114 patients in the HDT + ASCT arm.
	• 67 Patients were excluded from analysis;
	  ◦ 28 patients were not analysed in IFN arm: 20 did not receive assigned therapy, 1 patient had an Ann Arbor stage I or II, 3 abort of induction in remission; 1 radiation in remission.
	  ◦ 39 patients were not analysed in HDT + ASCT arm: 35 did not receive assigned therapy; 4 abort of induction in remission.
	• Baseline patient characteristics described.
	• Staging: clinical examination, complete blood count, serum biochemistry profile, chest radiography, abdominal ultrasound, computed tomography of the neck, chest, and abdomen, and bone marrow biopsy. Staging was performed before therapy, after every second cycle of induction therapy, and before and after ASCT.
	• Median follow-up time: 50 months
	• ITT analysis

Participants	• Inclusion criteria: Untreated patients between 18 to 59 years of age with advanced Ann Arbor stage III and IV follicular lymphoma, mantle cell lymphoma, or lymphoplasmacytic lymphoma according to the current WHO classification. For this meta-analysis patients with FL were evaluated. Patients had to be in need of therapy as defined by one of the following: B symptoms, hematopoetic insufficiency progressive disease as defined by 50% progression in the past 6 months, or bulky disease • Exclusion criteria: Patients with the potential for curative radiation therapy and those with poor performance status (ECOG performance status greater than 2). Patients with seriously impaired cardiac, pulmonary, hepatic or renal function (creatinine > 2 mg/dL). • Stage IV: IFN-arm 93 (73.8%), HDT + ASCT arm 85 (74.6%) • FLIPI-Score: IFN-arm: low risk 74 (62.2%), low-intermediate risk 34 (28.6%), high-intermediate risk 11 (9.2%); HDT + ASCT arm: low risk 53 (54.1%), low-intermediate risk 38 (38.8), high-intermediate risk 7 (7.1%) • Mean age (range): IFN: 49.1 (26 to 59) years; HDT + ASCT arm: 49.1 (29 to 59). • Gender: chemotherapy: 56 males (44.4%), 70 females; HDT + ASCT arm: 62 males (54.4%), 52 females. • Similar baseline patients' characteristics in comparison arms.

Interventions	• Initially, patients were randomly assigned for cytoreductive therapy with CHOP (cyclophosphamide 750 mg/m^2 i.v., day 1; doxorubicin 50 mg/m^2 i.v., day 1; vincristine 1.4 mg/m^2 [maximum, 2 mg] i.v., day 1; and prednisone 100 mg/m^2 orally, days 1 to 5) or with MCP (mitoxantrone 8 mg/m^2 i.v., days 1 to 2; chlorambucil 3 x 3 mg/m^2 orally , days1 to 5; and prednisone 25 mg/m^2 orally, days 1 to 5). Beginning in July 1998, all patients received CHOP because a randomised comparison of CHOP with MCP showed that MCP was associated with a significant impairment of hematopoietic stem cell mobilization. After 2 cycles of therapy, patients were randomly assigned to myeloablative radiochemotherapy followed by ASCT or to IFN-maintenance after the completion of induction therapy. Patients achieving CR after 4 cycles of initial cytoreductive chemotherapy immediately proceeded to consolidation therapy. All other patients received 6 cycles of induction therapy. Patients who had progressive disease during induction therapy or who did not achieve at least partial remission after the completion of induction therapy were removed from the study.
	• Intervention after randomisation:
	  • IFN-arm: 2 additional courses of conventional chemotherapy to balance the mobilization scheme (Dexa-BEAM). Subsequently, alpha-interferon was applied at a dose of 5 x 10^6 units s.c. 3 times weekly until progression.
	  • HDT + ASCT arm: Dexa-BEAM (dexamethasone 3 x 8 mg orally , days 1 to 10;cBCNU 60 mg/m2 i.v., day 2; melphalan 20 mg/m2 i.v., day 3; etoposide 75 mg/m2 i.v., days 4-7; cytarabine 2 100 mg/m2 i.v., days 4-7; and G-CSF initiated on day 11). Peripheral stem cells were harvested and subse-

GLSG *(Continued)*

	quently cryopreserved without any purging procedure. At least 2.0 106/kg body weight CD34 cells (and 2.0 106/kg body weight CD34 cells as back-up) were required for ASCT. Myeloablative therapy was performed within 2 months of mobilization and consisted of a combined TBI (12 Gy; TBI was fractionated into 6 applications of 2 Gy on days 6 to 4; pulmonary dosage was limited to 8Gy) and cyclophosphamide (60 mg/kg body weight i.v., days 3 and 2) regimen. Previously harvested peripheral blood stem cells were re infused on day 0. G-CSF was initiated on day
Outcomes	• Primary trial endpoint was defined as PFS after the completion of induction therapy. • Secondary outcomes: Response to therapy, OS, toxicity
Notes	Treatment information: Beginning in July 1998, all patients received CHOP instead of MCP or CHOP because a randomised comparison of CHOP with MCP showed that MCP was associated with a significant impairment of hematopoietic stem cell mobilization.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Prospective randomised trial
Allocation concealment (selection bias)	Low risk	"Randomization was carried out centrally."
Blinding (performance bias and detection bias) patients	High risk	Usually trials evaluating stem cell transplantation are not blinded
Blinding (performance bias and detection bias) physicians	High risk	Usually trials evaluating stem cell transplantation are not blinded
Blinding (performance bias and detection bias) assessors	Unclear risk	No information about blinding of the assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis (patients excluded from analysis who did not receive assigned therapy : 55 of 307 patients)
Selective reporting (reporting bias)	Unclear risk	No protocol is available.
Other bias	Unclear risk	"Beginning in July 1998, all patients received CHOP because a randomised comparison of CHOP with MCP showed that MCP was associated with a significant impairment of hematopoietic stem cell mobilization."

GOELAMS 064

Methods	• Randomised controlled trial with two arms: chemotherapy arm and HDT + ASCT arm. • Conducted by the Groupe Ouest-Est des Leuce´amies et des Autres Maladies du Sang (GOELAMS), 172 patients from 25 centres in France were enrolled. • Recruitment period from April 1994 to May 2001. • Of the 172 Patients, 166 were randomised 1:1; 80 to arm and CHVP 86 to HDT + ASCT-arm; 6 patients were not randomised: 4 after the pathology review, 1 by an investigator's decision, and 1 who declined to undergo randomisation.

GOELAMS 064 *(Continued)*

	• Baseline patient characteristics described. • Staging:a full review of the medical history, physical examination, routine laboratory tests and bone marrow biopsy was performed at diagnosis, as well as evaluations for abdominal and thoracic involvement by computed tomography imaging and/or ultrasonography. • Median follow-up time: 108 months. • ITT analysis.
Participants	• Inclusion criteria: Patients 18 to 60 years old with previously untreated histologically proven follicular lymphoma, classified according to the Working-Formulation criteria of the National Cancer Institute and reviewed according to the REAL classification. Ann Arbor stage of II to IV and a high tumour burden defined according to the GELF criteria. Patients with grade 3b FL were included. Measurable disease, the absence of underlying organ dysfunction precluding the use of anthracycline or high-dose chemotherapy, and the absence of human immunodeficiency virus infection were also required. • Exclusion criteria: Patients with transformed lymphoma were excluded. • Histology: CHVP arm: Grade 1: 40, Grade 2: 38 Grade 3: 2; HDT + ASCT arm: Grade 1: 28, Grade 2: 50, Grade 3: 8 • FLIPI-Score: CHVP-arm: low risk 23, intermediate risk 31, high risk 26; HDT + ASCT arm: low risk 26, intermediate risk 40, high risk 20 • Mean age (range):CHVP-arm: 50 (29-61) years; HDT + ASCT arm: 51 (32 to 60). • Gender: CHVP-arm: 47 males, 33 females; HDT + ASCT arm: 38 males, 48 females. • Similar baseline patient's characteristics in comparison arms

Interventions	• Conventional chemotherapy arm:
	  ◦ CHVP regimen, consisted of cyclophosphamide (600 mg/m^2), doxorubicin (25 mg/m^2), and teniposide (60 mg/m^2), all administered i.v. on day 1, and prednisone (40mg/m^2) p.o. on days 1 to 5. Treatment consisted of a 6 course induction phase administered monthly, followed, for responders and patients presenting a stable disease, by a maintenance phase that consisted of 1 cycle every 2 month for 1 year. Concomitant s.c. interferon α-2b was administered at 5x10^6 3 times a week for 18 months.
	• HDT+ ASCT arm:
	  ◦ VCAP (cyclophosphamide, high-dose doxorubicin, prednisone, and vincristine) regimen as first-line therapy combining vincristine (3 mg/m^2) on day 1, cyclophosphamide (1500 mg/m^2) on day 2, doxorubicin (80 mg/m^2) on day 2, and prednisone (50 mg/m^2) on day 1 to 5, every three weeks. Patients in CR, VGPR, or PR after the second or third VCAP cycle continued on to stem-cell harvesting and received, before transplantation, one course of IMVP16 (ifosamide, methotrexate, and VP-16), which combined ifosamide (1.5 g/m^2) and VP-16 (100 mg/m^2) on days 1 through 3, and methotrexate (30 mg/m^2) on days 1 to 10. Patients with less than PR after the VCAP cycles received, as salvage therapy, 2 to 3 courses of DHAP (dexamethasone, high-dose cytarabine, and cisplatin) combining cisplatine (100 mg/m^2) on day 1, cytarabine (4 g/m^2) on day 2, and dexamethasone (40 mg/m^2) on days 1 through 4. If at least a PR was obtained after DHAP, stem cells were harvested or patients were considered as failures. Conditioning regimen started 4 to 6 weeks after the IMVP 16 or the last DHAP cycle in responding patients and included cyclophosphamide (60 mg/kg body weight) infused on each of 2 consecutive days after TBI, administered in fractionated doses (200 cGy) twice daily on 3 consecutive days in all pat. Stem cells were re-infused within 48 hours of the completion of the conditioning regimen.
	  ◦ Radiotherapy: TBI, administered in fractionated doses (200 cGy) twice daily on 3 consecutive days in all pat.(on day -6 to -4).
	• Important treatment information: If the graft did not contain at least 1x10^4 granulocyte-macrophage colony-forming units (CFU-GMs) for marrow and more than 2x10^4 for peripheral blood stem cells, the procedure was considered to have failed, patients were not given transplants, and patients then received treatment according to the local investigators decision.

Outcomes	This study was designed by the GOELAMS Lymphoma Committee with the aim of detecting a 25% absolute difference in EFS at 3 years Secondary end points were the response rate at the end of treatment, the OS rate, and the incidence of adverse effects. • Primary outcome: EFS

GOELAMS 064 *(Continued)*

- Secondary outcomes: OS, RR, adverse events, secondary malignancies

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"a randomised multicenter study"
Allocation concealment (selection bias)	Low risk	"Randomization was carried out centrally, and was stratified according to each center."
Blinding (performance bias and detection bias) patients	High risk	Usually trials evaluating stem cell transplantation are not blinded
Blinding (performance bias and detection bias) physicians	High risk	Usually trials evaluating stem cell transplantation are not blinded
Blinding (performance bias and detection bias) assessors	Unclear risk	No information about blinding of the assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis
Selective reporting (reporting bias)	Low risk	Protocol available at www.controlled-trials.com/mrct/trial/printfriendly/450205
Other bias	Low risk	Tthe trial seems free of other bias

aaPI: age-adjusted International Prognostic Index; ASCT: stem cell transplantation; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; CHVP: cyclophosphamide, doxorubicin, teniposide, and prednisolone; CNS: central nevous system; CR: complete response; Cy: cyclophosphamide; DFS: Disease-free survival; ECOG: Eastern Cooperative Oncology Group; EFS: event-free survival; FL: follicular lymphoma; G-CSF: Granulocyte colony-stimulating factor; HBV: hepatitis B virus; HDT: high-dose therapy; HIV: Human immunodeficiency virus; IFN: interferon; ITT: intention-to-treat; LDH: i.v. intravenous; Lactate dehydrogenase; NHL: non-Hodgkin`s lymphoma; OS: overall survival; PBSC: peripheral blood stem cells; PFS: progression-free survival; p.o.: orally; PR: partial response; PS: performance status; RR: response rate; s.c.: subcutaneous; TBI: total body irradiation; WHO: World Health Organization.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Baldissera 2006	Patients with aggressive high-risk NHL, and not FL, were randomised.
Brice 2000	Not a randomised controlled trial. Patients were analysed retrospectively.
Cao 2001	Not a randomised controlled trial. Patients were analysed retrospectively.
De Souza 2003	Patients with aggressive high-risk NHL, and not FL, were randomised
De Souza 2004	Patients with aggressive high-risk NHL, and not FL, were randomised

Study	Reason for exclusion
Gianni 1997	Patients with diffuse large-cell lymphoma, and not FL, were randomised.
Guglielmi 1993	Patients with aggressive NHL, and not FL, were randomised.
Hagenbeek 1991	Patients with aggressive NHL, and not FL were randomised.
Haioun 1993	Patients with aggressive NHL, and not FL, were randomised.
Haioun 1994	Patients with aggressive high-risk NHL, and not FL, were randomised.
Haioun 1997	Patients with aggressive NHL, and not FL, were randomised.
Intragumtornchai 2000	Patients with aggressive NHL, and not FL, were randomised.
Intragumtornchai 2006	Patients with aggressive NHL, and not FL, were randomised.
Kaiser 2002	Patients with aggressive NHL, and not FL, were randomised.
Kluin-Nelemans 2001	Patients with aggressive NHL, and not FL, were randomised.
Leppa 2006	Patients with FL were randomised to rituximab maintenance treatment or to observation.
Marin 2001	No randomised controlled trial.
Martelli 1996	Patients with aggressive NHL, and not FL, were randomised.
Martelli 1999	Patients with aggressive NHL, and not FL, were randomised.
Martelli 2003	Not a randomised controlled trial.
Martinez 1995	Not a randomised controlled trial.
McBride 1996	Not a randomised controlled trial.
Metzner 2002	Not a randomised controlled trial.
Moser 2005	Patients with aggressive NHL were analysed.
Mounier 2000	Patients with aggressive NHL, and not FL, were randomised.
Olivieri 2005	Patients with aggressive NHL, and not FL, were randomised
Pettengell 1996	No randomised controlled trial. Patients with FL not mentioned separately.
Philip 1991	Patients with FL not mentioned separately.
Philip 1995	Patients with FL not mentioned separately.
Philip 1995a	Patients with FL not mentioned separately.
Proctor 2003	Patients with aggressive NHL, and not FL, were randomised.
Rabinowe 1990	All randomised patients were treated with autologous bone marrow transplantation.
Rohatiner 1991	Not a randomised controlled trial.

Study	Reason for exclusion
Rohatiner 1994	Not a randomised controlled trial.
Rohatiner 1994a	Not a randomised controlled trial.
Santini 1991	Not a randomised controlled trial.
Santini 1997	Patients with follicular lymphoma not mentioned separately.
Santini 1998	Patients with aggressive NHL, and not follicular lymphoma, were randomised.
Sonnen 1998	Not a randomised controlled trial.
Sweetenham 2001	Patients with lymphoblastic lymphoma, and not FL, were randomised.
Winter 2005	Not a randomised controlled trial.

FL: follicular lymphoma; NHL: non-Hodgkin`s lymphoma.

DATA AND ANALYSES

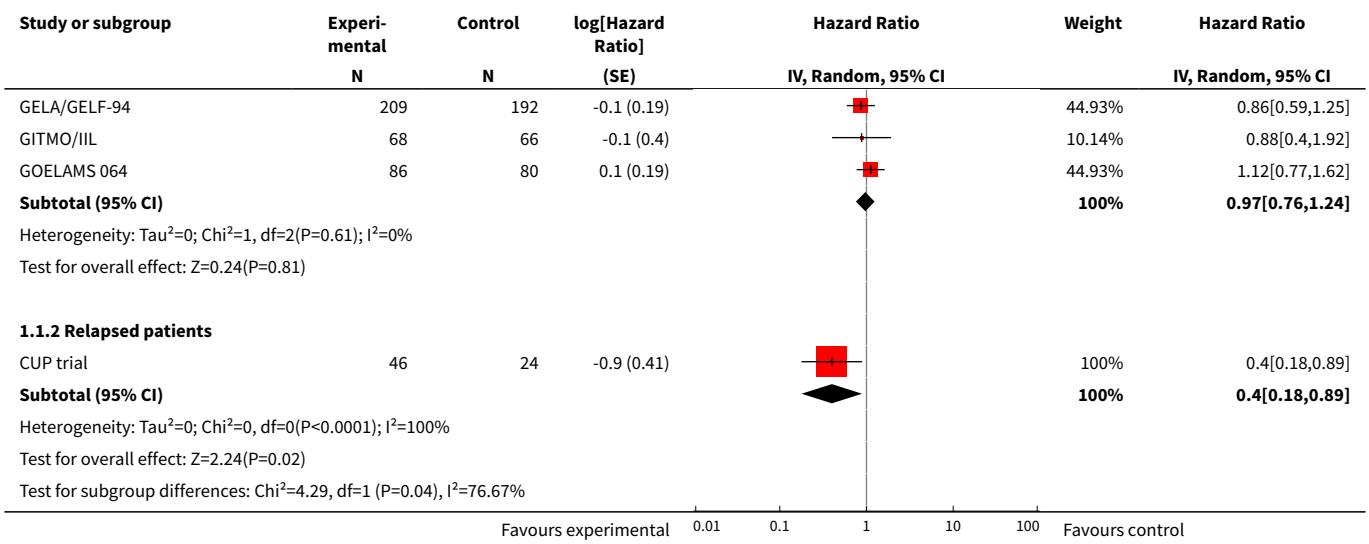
Comparison 1. Overall survival

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Stage of disease	4		Hazard Ratio (Random, 95% CI)	Subtotals only
1.1 Untreated patients	3	701	Hazard Ratio (Random, 95% CI)	0.97 [0.76, 1.24]
1.2 Relapsed patients	1	70	Hazard Ratio (Random, 95% CI)	0.40 [0.18, 0.89]
2 Rituximab-containing regimen (previously untreated patients)	3	701	Hazard Ratio (Random, 95% CI)	0.97 [0.76, 1.24]
2.1 Rituximab in both arms	1	134	Hazard Ratio (Random, 95% CI)	0.88 [0.40, 1.92]
2.2 No rituximab in both arms	2	567	Hazard Ratio (Random, 95% CI)	0.98 [0.75, 1.28]

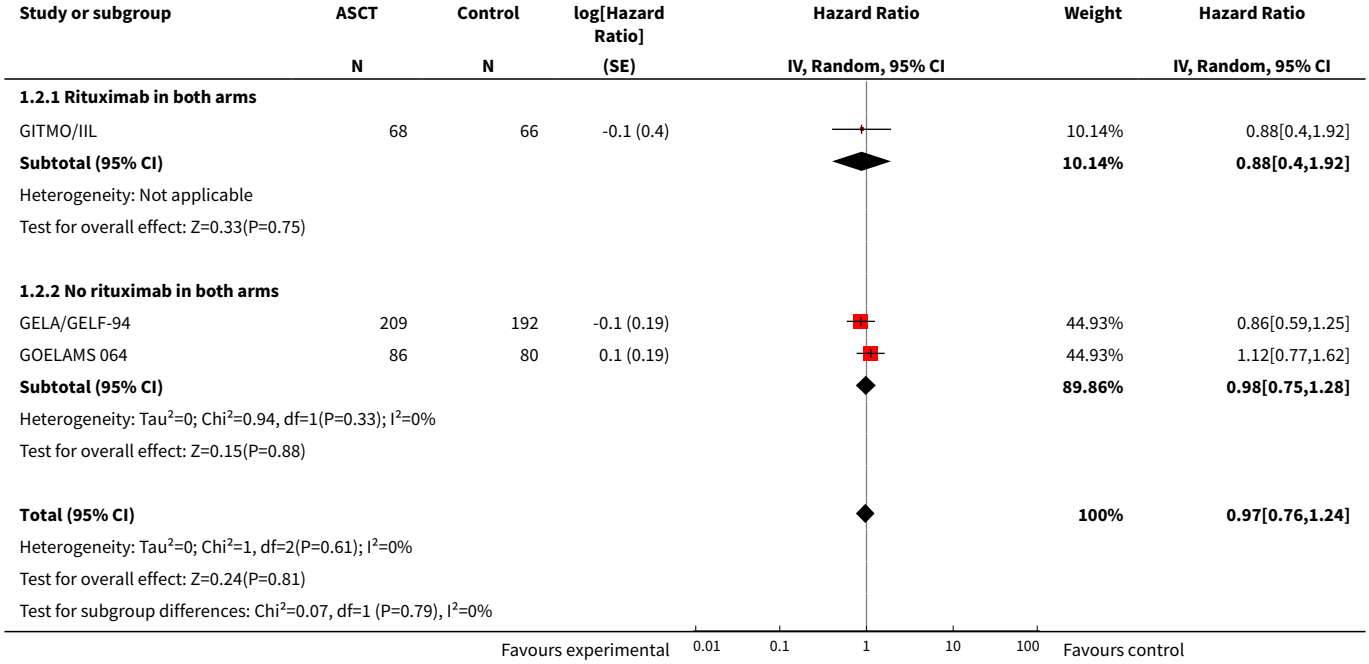
Analysis 1.1. Comparison 1 Overall survival, Outcome 1 Stage of disease.

Study or subgroup	Experimental	Control	log[Hazard Ratio]	Hazard Ratio	Weight	Hazard Ratio
	N	N	(SE)	IV, Random, 95% CI		IV, Random, 95% CI
1.1.1 Untreated patients						

Favours experimental 0.01 0.1 1 10 100 Favours control



Analysis 1.2. Comparison 1 Overall survival, Outcome 2 Rituximab-containing regimen (previously untreated patients).



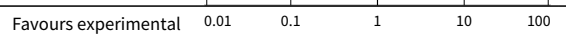
Comparison 2. Progression-free survival

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Stage of disease	4		Hazard Ratio (Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Untreated patients	3	540	Hazard Ratio (Random, 95% CI)	0.42 [0.33, 0.54]
1.2 Relapsed patients	1	70	Hazard Ratio (Random, 95% CI)	0.30 [0.15, 0.61]
2 Rituximab-containing regimen (previously untreated patients)	3	540	Hazard Ratio (Random, 95% CI)	0.42 [0.33, 0.54]
2.1 Rituximab in both arms	1	134	Hazard Ratio (Random, 95% CI)	0.36 [0.23, 0.55]
2.2 No rituximab in both arms	2	406	Hazard Ratio (Random, 95% CI)	0.46 [0.33, 0.63]

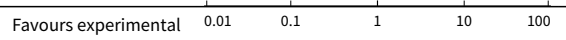
Analysis 2.1. Comparison 2 Progression-free survival, Outcome 1 Stage of disease.

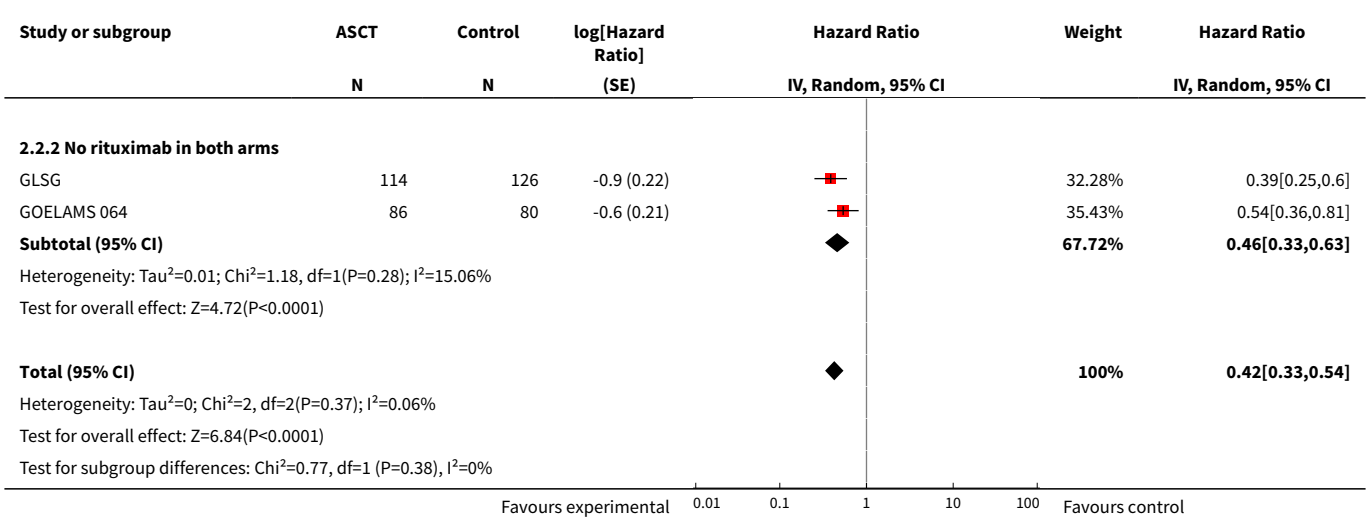
Study or subgroup	Experimental N	Control N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Random, 95% CI	Weight	Hazard Ratio IV, Random, 95% CI
2.1.1 Untreated patients						
GITMO/IIL	68	66	-1 (0.22)		32.28%	0.36[0.23,0.55]
GLSG	114	126	-0.9 (0.22)		32.28%	0.39[0.25,0.6]
GOELAMS 064	86	80	-0.6 (0.21)		35.43%	0.54[0.36,0.81]
Subtotal (95% CI)					**100%**	**0.42[0.33,0.54]**
Heterogeneity: Tau^2=0; Chi^2=2, df=2(P=0.37); I^2=0.06%						
Test for overall effect: Z=6.84(P<0.0001)						
2.1.2 Relapsed patients						
CUP trial	46	24	-1.2 (0.36)		100%	0.3[0.15,0.61]
Subtotal (95% CI)					**100%**	**0.3[0.15,0.61]**
Heterogeneity: Not applicable						
Test for overall effect: Z=3.33(P=0)						
Test for subgroup differences: Chi^2=0.82, df=1 (P=0.37), I^2=0%						



Analysis 2.2. Comparison 2 Progression-free survival, Outcome 2 Rituximab-containing regimen (previously untreated patients).

Study or subgroup	ASCT N	Control N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Random, 95% CI	Weight	Hazard Ratio IV, Random, 95% CI
2.2.1 Rituximab in both arms						
GITMO/IIL	68	66	-1 (0.22)		32.28%	0.36[0.23,0.55]
Subtotal (95% CI)					**32.28%**	**0.36[0.23,0.55]**
Heterogeneity: Not applicable						
Test for overall effect: Z=4.64(P<0.0001)						

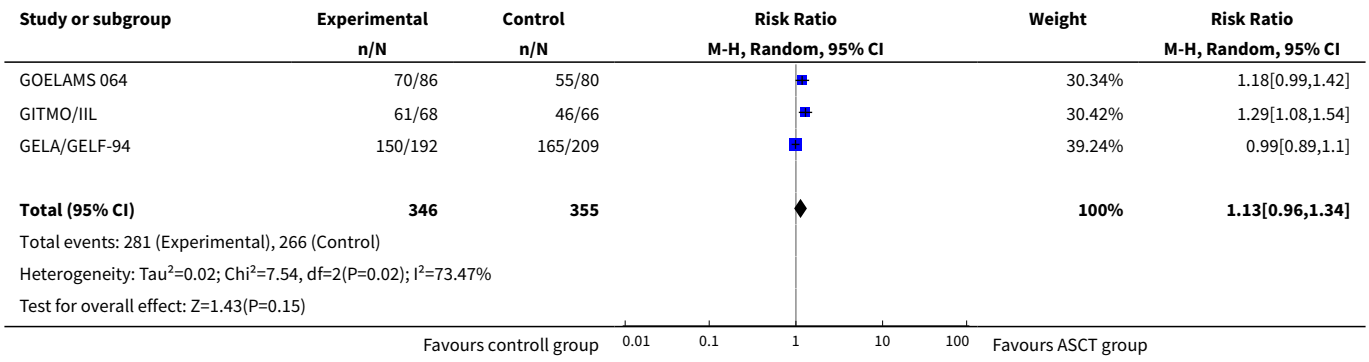




Comparison 3. Overall response rate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All trials (previously untreated patients)	3	701	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.96, 1.34]
2 Rituximab-containing regimen (previously untreated patients)	3	701	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.96, 1.34]
2.1 Rituximab in both arms	1	134	Risk Ratio (M-H, Random, 95% CI)	1.29 [1.08, 1.54]
2.2 No rituximab in both arms	2	567	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.90, 1.27]

Analysis 3.1. Comparison 3 Overall response rate, Outcome 1 All trials (previously untreated patients).



Analysis 3.2. Comparison 3 Overall response rate, Outcome 2 Rituximab-containing regimen (previously untreated patients).

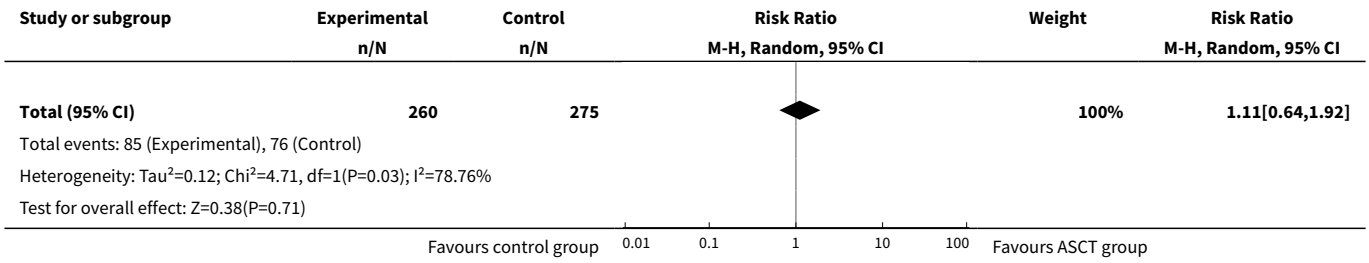
Study or subgroup	ASCT n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 Rituximab in both arms					
GITMO/IIL	61/68	46/66		30.42%	1.29[1.08,1.54]
Subtotal (95% CI)	**68**	**66**		**30.42%**	**1.29[1.08,1.54]**
Total events: 61 (ASCT), 46 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.77(P=0.01)					
3.2.2 No rituximab in both arms					
GELA/GELF-94	150/192	165/209		39.24%	0.99[0.89,1.1]
GOELAMS 064	70/86	55/80		30.34%	1.18[0.99,1.42]
Subtotal (95% CI)	**278**	**289**		**69.58%**	**1.07[0.9,1.27]**
Total events: 220 (ASCT), 220 (Control)					
Heterogeneity: Tau^2=0.01; Chi^2=2.92, df=1(P=0.09); I^2=65.8%					
Test for overall effect: Z=0.72(P=0.47)					
Total (95% CI)	**346**	**355**		**100%**	**1.13[0.96,1.34]**
Total events: 281 (ASCT), 266 (Control)					
Heterogeneity: Tau^2=0.02; Chi^2=7.54, df=2(P=0.02); I^2=73.47%					
Test for overall effect: Z=1.43(P=0.15)					
Test for subgroup differences: Chi^2=2.21, df=1 (P=0.14), I^2=54.72%					

Comparison 4. Complete response rate

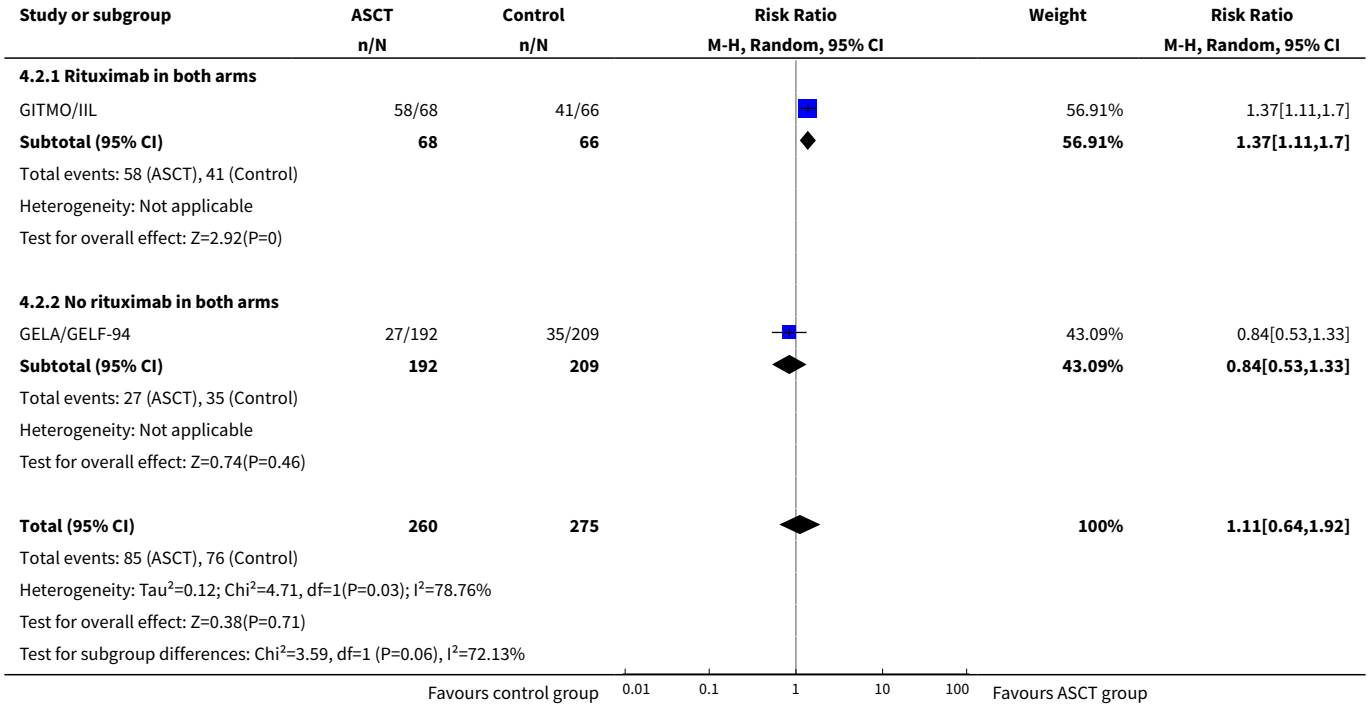
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All trials (previously untreated patients)	2	535	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.64, 1.92]
2 Rituximab-containing regimen (previously untreated patients)	2	535	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.64, 1.92]
2.1 Rituximab in both arms	1	134	Risk Ratio (M-H, Random, 95% CI)	1.37 [1.11, 1.70]
2.2 No rituximab in both arms	1	401	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.53, 1.33]

Analysis 4.1. Comparison 4 Complete response rate, Outcome 1 All trials (previously untreated patients).

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
GELA/GELF-94	27/192	35/209		43.09%	0.84[0.53,1.33]
GITMO/IIL	58/68	41/66		56.91%	1.37[1.11,1.7]



Analysis 4.2. Comparison 4 Complete response rate, Outcome 2 Rituximab-containing regimen (previously untreated patients).



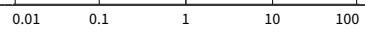
Comparison 5. Treatment-related mortality

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All trials (previously untreated patients)	4	941	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.25, 6.61]
2 Rituximab-containing regimen (previously untreated patients)	4	941	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.25, 6.61]
2.1 Rituximab in both arms	1	134	Risk Ratio (M-H, Random, 95% CI)	1.46 [0.25, 8.44]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 No rituximab in both arms	3	807	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.04, 26.11]

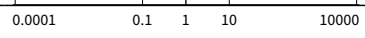
Analysis 5.1. Comparison 5 Treatment-related mortality, Outcome 1 All trials (previously untreated patients).

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
GELA/GELF-94	0/192	3/209		22.64%	0.16[0.01,2.99]
GITMO/IIL	3/68	2/66		43.21%	1.46[0.25,8.44]
GLSG	4/114	1/126		34.15%	4.42[0.5,38.98]
GOELAMS 064	0/86	0/80			Not estimable
Total (95% CI)	**460**	**481**		**100%**	**1.28[0.25,6.61]**
Total events: 7 (Experimental), 6 (Control)					
Heterogeneity: Tau²=0.82; Chi²=3.25, df=2(P=0.2); I²=38.52%					
Test for overall effect: Z=0.3(P=0.77)					



Analysis 5.2. Comparison 5 Treatment-related mortality, Outcome 2 Rituximab-containing regimen (previously untreated patients).

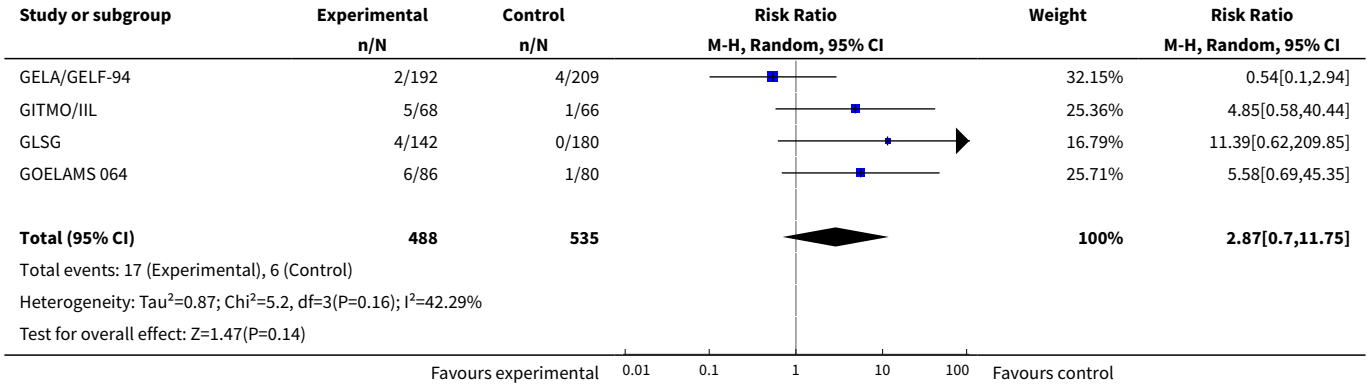
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.2.1 Rituximab in both arms					
GITMO/IIL	3/68	2/66		43.21%	1.46[0.25,8.44]
Subtotal (95% CI)	**68**	**66**		**43.21%**	**1.46[0.25,8.44]**
Total events: 3 (Experimental), 2 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.42(P=0.68)					
5.2.2 No rituximab in both arms					
GELA/GELF-94	0/192	3/209		22.64%	0.16[0.01,2.99]
GLSG	4/114	1/126		34.15%	4.42[0.5,38.98]
GOELAMS 064	0/86	0/80			Not estimable
Subtotal (95% CI)	**392**	**415**		**56.79%**	**0.97[0.04,26.11]**
Total events: 4 (Experimental), 4 (Control)					
Heterogeneity: Tau²=3.95; Chi²=3.25, df=1(P=0.07); I²=69.26%					
Test for overall effect: Z=0.02(P=0.98)					
Total (95% CI)	**460**	**481**		**100%**	**1.28[0.25,6.61]**
Total events: 7 (Experimental), 6 (Control)					
Heterogeneity: Tau²=0.82; Chi²=3.25, df=2(P=0.2); I²=38.52%					
Test for overall effect: Z=0.3(P=0.77)					
Test for subgroup differences: Chi²=0.05, df=1 (P=0.83), I²=0%					



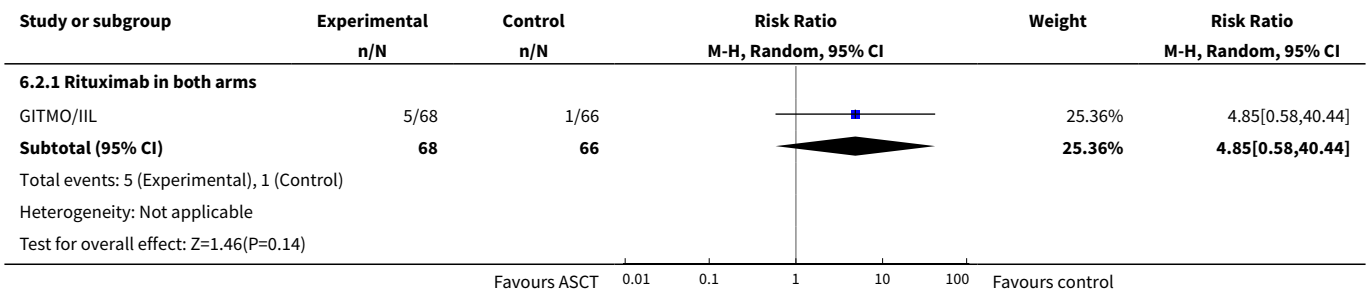
Comparison 6. Secondary malignancies (previously untreated patients)

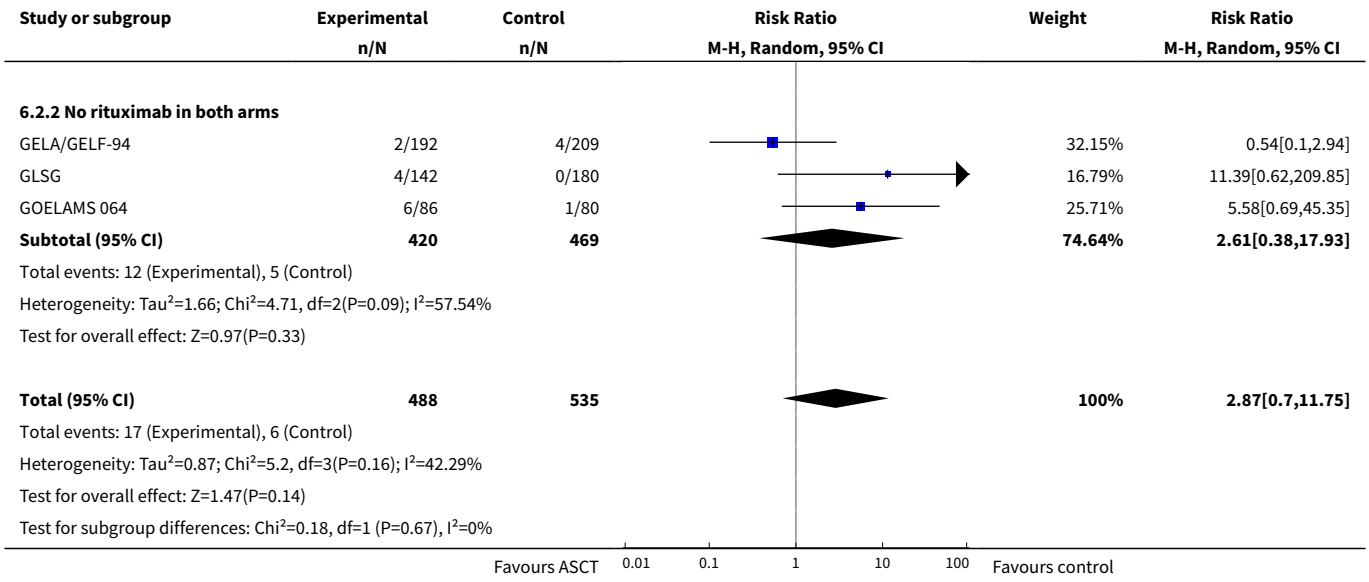
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 AML/MDS	4	1023	Risk Ratio (M-H, Random, 95% CI)	2.87 [0.70, 11.75]
2 AML/MDS/ rituximab-containing regimen	4	1023	Risk Ratio (M-H, Random, 95% CI)	2.87 [0.70, 11.75]
2.1 Rituximab in both arms	1	134	Risk Ratio (M-H, Random, 95% CI)	4.85 [0.58, 40.44]
2.2 No rituximab in both arms	3	889	Risk Ratio (M-H, Random, 95% CI)	2.61 [0.38, 17.93]
3 Solid cancer	3	701	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.25, 5.77]
4 Solid cancer/ rituximab-containing regimen	3	701	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.25, 5.77]
4.1 Rituximab in both arms	1	134	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.03, 3.03]
4.2 No rituximab in both arms	2	567	Risk Ratio (M-H, Random, 95% CI)	2.44 [0.20, 29.93]

Analysis 6.1. Comparison 6 Secondary malignancies (previously untreated patients), Outcome 1 AML/MDS.

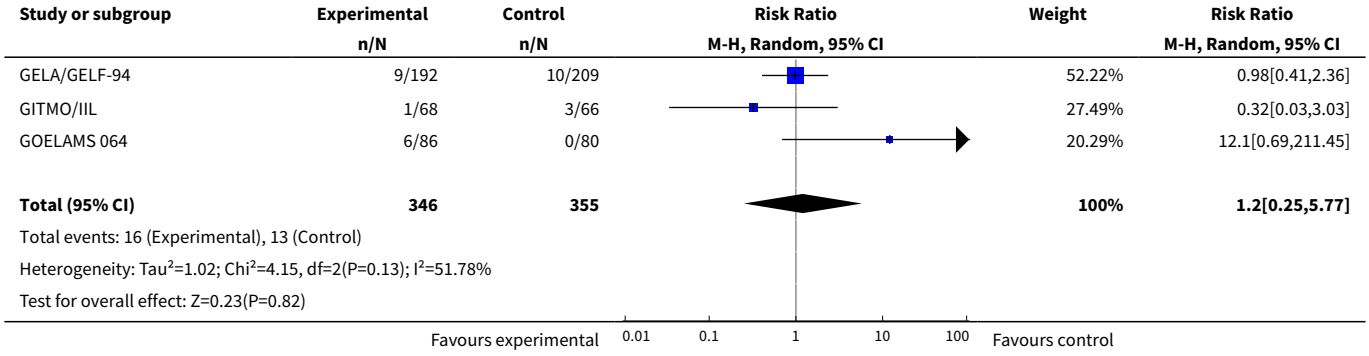


Analysis 6.2. Comparison 6 Secondary malignancies (previously untreated patients), Outcome 2 AML/MDS/ rituximab-containing regimen.

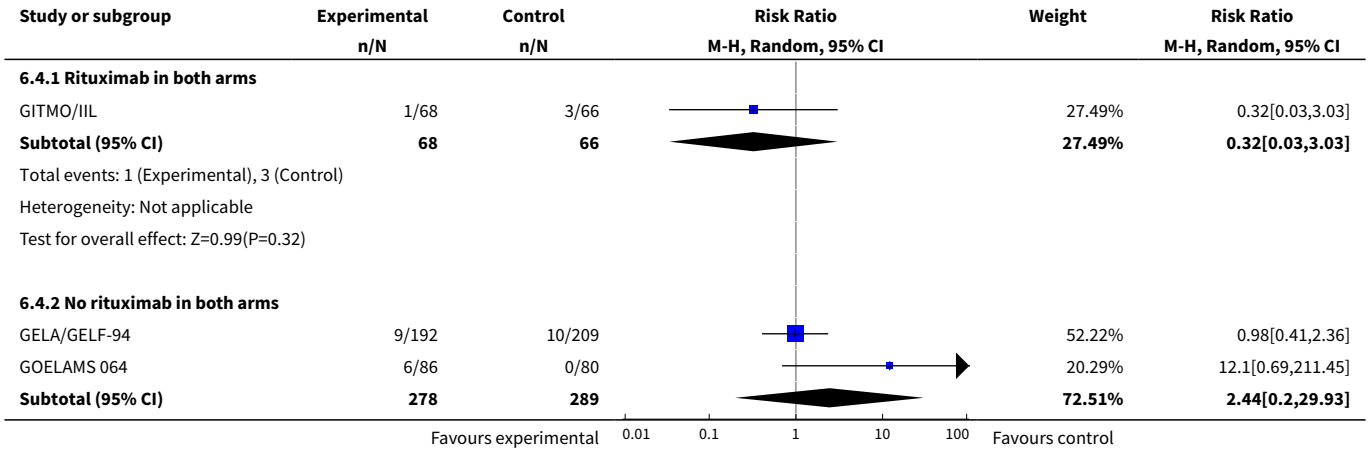


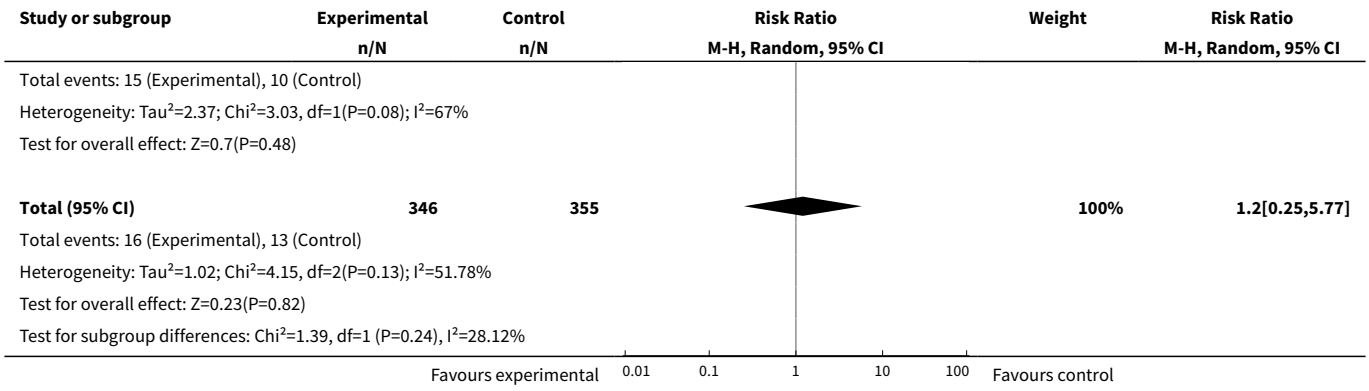


Analysis 6.3. Comparison 6 Secondary malignancies (previously untreated patients), Outcome 3 Solid cancer.



Analysis 6.4. Comparison 6 Secondary malignancies (previously untreated patients), Outcome 4 Solid cancer/ rituximab-containing regimen.





ADDITIONAL TABLES

Table 1. Adverse Events

	CUP trial	GLGSG trial	GITMO/IIL	GOELAMS	GELA/GELF 94
Number of patients evaluated	**ASCT arm: 46** **CT arm: 24**	**ASCT arm: 105** **CT arm: 122**	**ASCT arm: 68** **CT arm: 66**	**ASCT arm: 86** **CT arm: 80**	**ASCT arm: 209** **CT arm: 192**
Anemia	N.R.	ASCT arm: 44.8% CT arm: 0.8%	N.R.	N.R.	N.R.
Leucocytopenia	N.R.	ASCT arm: 96.2% CT arm: 51.3%	N.R.	N.R.	N.R.
Granulocytopenia	N.R.	ASCT arm: 90.5% CT arm: 37.8%	N.R.	N.R.	N.R.
Thrombocytopenia	N.R.	ASCT arm: 96.2% CT arm: 4.2%	N.R.	N.R.	N.R.
Mucositis	N.R.	ASCT arm: 53.3% CT arm: 0	N.R.	N.R.	N.R.
Infections	N.R.	ASCT arm: 23.1% CT arm: 1.7%	ASCT arm: 13.2% CT arm: 6.1%	ASCT arm: 17.4% CT arm: N.R.	N.R.
Nausea	N.R.	ASCT arm: 32.4% CT arm: 1.7%	N.R.	N.R.	N.R.
diarrhoea	N.R.	ASCT arm: 13.5% CT arm: 1.7%	N.R.	N.R.	N.R.

Table 1. Adverse Events *(Continued)*

pulmonary	N.R.	ASCT arm: 4.8% CT arm: 0.9%	N.R.	ASCT arm: 2.3% interstitial pneumonitis CT arm: N.R.	N.R.
liver	N.R.	ASCT arm: 3.8% CT arm: 0.9%	N.R.	N.R.	N.R.
Renal	N.R.	ASCT arm: 1% CT arm: 0	N.R.	ASCT arm: 1.2% haemorrhagic cystitis CT arm: N.R.	N.R.
muscle/bone pain	N.R.	ASCT arm: 2.1% CT arm: 11%	N.R.	N.R.	N.R.
Depression	N.R.	ASCT arm: 1.1% CT arm: 4.9%	N.R.	N.R.	N.R.
Extrahematological toxicities	N.R.	mentioned above	ASCT arm: 38.2% CT arm: 10.6%	mentioned above	N.R.

APPENDICES

Appendix 1. CENTRAL search strategy to November 2010

#1 MeSH descriptor Lymphoma, Follicular explode all trees

#2 (follicul* NEAR/2 lymph*)

#3 (nodular* NEAR/2 lymph*)

#4 ((small* OR large*) NEAR/4 follicul*)

#5 ((small* OR large*) NEAR/4 lymph*)

#6 ((low-grad* OR low grad*) NEAR/ lymph*)

#7 ((low-grad* OR low grad*) AND lymph*)

#8 (centro blast* OR zentroblast*)

#9 (follic* NEAR/2 (center* OR centro*) NEAR/ lymph*)

#10 (brill-symmer* OR brill symmer*)

#11 MeSH descriptor Lymphoma, B-Cell, this term only

#12 (indolent* NEAR/2 lymph*)

#13 MeSH descriptor Lymphoma, Non-Hodgkin explode all trees

#14 (non-hodgkin* OR nonhodgkin* OR non hodgkin*)

#15 (diffus* NEAR/ lymphom*)

#16 (lymphati* sacrom* OR lymphosarcom*)

#17 MeSH descriptor Hematologic Neoplasms explode all trees

#18 (hemato* NEAR/ (malign* OR neoplas*))

#19 (haemato* NEAR/ (malign* OR neoplas*))

#20 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16) delete

#21 (#17 OR #18 OR #19)

#22 MeSH descriptor Transplantation, Autologous explode all trees

#23 (autolog* NEAR/4 (transplant* OR graft*))

#24 (asct)

#25 (autograft* OR auto-graft*)

#26 (autotransplant* OR auto-transplant*)

#27 (#22 OR #23 OR #24 OR #25 OR #26)

#28 MeSH descriptor Transplantation Conditioning explode all trees

#29 (myeloablativ*)

#30 (#28 OR #29)

#31 (#20 AND (#27 OR #30)) 351 (295 hits in CENTRAL)

Appendix 2. CENTRAL search strategy from November 2010 to September 2011

#1 MeSH descriptor Lymphoma, Follicular explode all trees

#2 (follicul* NEAR/2 lymph*)

#3 (nodular* NEAR/2 lymph*)

#4 ((small* OR large*) NEAR/4 follicul*)

#5 ((small* OR large*) NEAR/4 lymph*)

#6 ((low-grad* OR low grad*) NEAR/ lymph*)

#7 ((low-grad* OR low grad*) AND lymph*)

#8 (centro blast* OR zentroblast*)

#9 (follic* NEAR/2 (center* OR centro*) NEAR/ lymph*)

#10 (brill-symmer* OR brill symmer*)

#11 MeSH descriptor Lymphoma, B-Cell, this term only

#12 (indolent* NEAR/2 lymph*)

#13 MeSH descriptor Lymphoma, Non-Hodgkin explode all trees

#14 (non-hodgkin* OR nonhodgkin* OR non hodgkin*)

#15 (diffus* NEAR/ lymphom*)

#16 (lymphati* sacrom* OR lymphosarcom*)

#17 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16)

#18 MeSH descriptor Transplantation, Autologous explode all trees

#19 (autolog* NEAR/4 (transplant* OR graft*))

#20 (asct)

#21 (autograft* OR auto-graft*)

#22 (autotransplant* OR auto-transplant*)

#23 (#18 OR #19 OR #20 OR #21 OR #22)

#24 MeSH descriptor Transplantation Conditioning explode all trees

#25 (myeloablativ*)

#26 (#24 OR #25)

#27 (#17 AND (#23 OR #26))

#28 (#27), from 2011 to 2011

Appendix 3. MEDLINE search strategy

1. Lymphoma, Follicular/

2. (follicul$ adj2 lymph$).tw,kf,ot.

3. (nodular$ adj2 lymph$).tw,kf,ot.

4. ((small$ or large$) adj4 (follicul$ adj2 lymph$)).tw,kf,ot.

5. ((low-grad$ or low grad$) adj lymph$).tw,kf,ot.

6. ((centro blast$ or zentroblast$) adj (centrocyst$ or zentrozyt$) adj lymph$).tw,kf,ot.

7. (follic$ adj2 (center$ or centro$) adj lymph$).tw,kf,ot.

8. (brill-symmer$ or brill symmer$).tw,kf,ot.

9. *Lymphoma, B-Cell/

10. (indolent$ adj2 lymph$).tw,kf,ot.

11. exp Lymphoma, Non-Hodgkin/

12. (non-hodgkin$ or nonhodgkin$ or non hodgkin$).tw,kf,ot.

13. (diffus$ adj lymphom$).tw,kf,ot.

14. (lymphati$ sacrom$ or lymphosarcom$).tw,kf,ot.

15. or/1-14

16. exp Transplantation, Autologous/

17. (autolog$ adj4 (transplant$ or graft$)).tw,kf,ot.

18. asct.tw.

19. (autograft$ or auto-graft$).tw,kf,ot.

20. (autotransplant$ or auto-transplant$).tw,kf,ot.

21. or/16-20

22. Transplantation Conditioning/

23. myeloablativ$.tw,kf,ot.

24. or/22-23

25. 21 or 24

26. randomized controlled trial.pt.

27. controlled clinical trial.pt.

28. randomized controlled trial/

29. random allocation/

30. double blind method/

31. single blind method/

32. or/26-31

33. (ANIMALS not HUMANS).sh.

34. 32 not 33

35. clinical trial.pt.

36. exp clinical trial/

37. (clin$ adj25 trial$).ti,ab.

38. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.

39. placebos/

40. placebo$.ti,ab.

41. random$.ti,ab.

42. research design/

43. or/35-42

44. 43 not 33

45. 44 not 34

46. comparative study/

47. exp evaluation studies/

48. follow up studies/

49. prospective studies/

50. (control$ or prospectiv$ or volunteer$).ti,ab.

51. or/46-50

52. 51 not 33

53. 52 not (34 or 45)

54. 34 or 45 or 53

55. randomized controlled trial.pt.

56. controlled clinical trial.pt.

57. randomized.ab.

58. drug therapy.fs.

59. randomly.ab.

60. trial.ab.

61. groups.ab.

62. or/55-61

63. humans.sh.

64. 62 and 63

65. 15 and (21 or 24)

66. 65 and 54 (1212)

67. 65 and 64

68. 66 not 67

69. 67 not 66 (405)

70. 66 or 69 (1617)

(51)

Appendix 4. EMBASE search strategy

1 FOLLICULAR LYMPHOMA/ (3145)

2 (follicul$ adj2 lymph$).tw. (3134)

3 (nodular$ adj2 lymph$).tw. (767)

4 ((small$ or large$) adj4 (follicul$ adj2 lymph$)).tw. (308)

5 ((low-grad$ or low grad$) adj lymph$).tw. (914)

6 ((centro blast$ or zentroblast$) adj (centrocyst$ or zentrozyt$) adj lymph$).tw. (0)

7 (follic$ adj2 (center$ or centro$) adj lymph$).tw. (154)

8 (brill-symmer$ or brill symmer$).tw. (12)

9 *B CELL LYMPHOMA/ (6685)

10 (indolent$ adj2 lymph$).tw. (500)

11 exp NONHODGKIN LYMPHOMA/ (53565)

12 (non-hodgkin$ or nonhodgkin$ or non hodgkin$).tw. (20573)

13 (diffus$ adj lymphom$).tw. (254)

14 (lymphati$ sacrom$ or lymphosarcom$).tw. (850)

15 or/1-14 (58499)

16 exp AUTOTRANSPLANTATION/ (5600)

17 (autolog$ adj4 (transplant$ or graft$)).tw. (12201)

18 asct.tw. (743)

19 (autograft$ or auto-graft$).tw. (6980)

20 (autotransplant$ or auto-transplant$).tw. (3189)

21 or/16-20 (23169)

22 MYELOABLATIVE CONDITIONING/ (696)

23 myeloablativ$.tw. (2264)

24 or/22-23 (2625)

25 21 or 24 (25151)

26 Clinical trial/ (505625)

27 Randomized controlled trial/ (158767)

28 RANDOMIZATION/ (25683)

29 SINGLE BLIND PROCEDURE/ (7603)

30 DOUBLE BLIND PROCEDURE/ (69545)

31 CROSSOVER PROCEDURE/ (20372)

32 PLACEBO/ (114333)

33 Randomi?ed controlled trial$.tw. (29147)

34 RCT.tw. (2297)

35 Random allocation.tw. (615)

36 Randomly allocated.tw. (9739)

37 Allocated randomly.tw. (1324)

38 (allocated adj2 random).tw. (553)

39 Single blind$.tw. (7178)

40 Double blind$.tw. (82249)

41 ((treble or triple) adj blind$).tw. (130)

42 Placebo$.tw. (105757)

43 PROSPECTIVE STUDY/ (75226)

44 or/26-43 (665188)

45 Case study/ (5522)

46 Case report.tw. (112827)

47 Abstract report/ or letter/ (469789)

48 or/45-47 (586070)

49 44 not 48 (642100)

50 animal/ (18243)

51 human/ (6155100)

52 50 not 51 (14469)

53 49 not 52 (642004)

54 15 and 25 and 53 (648)

CONTRIBUTIONS OF AUTHORS

Schaaf M: Abstract screening, data extraction, quality assessment (RoB), data analysis and interpretation, drafting of the review

Skoetz N: Drafting of the protocol, abstract screening, data extraction, data entry into RevMan, drafting of the review, data checking, communication between authors, proofreading, update screening

Reiser M: Clinical expertise, advice for the protocol

Borchmann P: Clinical expertise, content input and revising the final draft

Engert A: Clinical expertise, content input

DECLARATIONS OF INTEREST

None known.

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INDEX TERMS

Medical Subject Headings (MeSH)

Antibodies, Monoclonal, Murine-Derived [therapeutic use]; Antineoplastic Combined Chemotherapy Protocols [*therapeutic use]; Combined Modality Therapy [methods] [mortality]; Disease-Free Survival; Hematopoietic Stem Cell Transplantation [*methods]; Immunologic Factors [therapeutic use]; Lymphoma, Follicular [mortality] [*therapy]; Neoplasms, Second Primary [etiology]; Randomized Controlled Trials as Topic [mortality]; Recurrence; Rituximab; Transplantation, Autologous; Whole-Body Irradiation [*methods]

MeSH check words

Female; Humans