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Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma (Review)

Skoetz N, Will A, Monsef I, Brillant C, Engert A, von Tresckow B

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[Intervention Review]

Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

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ABSTRACT

Background

There are two different international standards for the treatment of early unfavourable and advanced stage Hodgkin lymphoma (HL): chemotherapy with escalated BEACOPP (bleomycin/etoposide/doxorubicin/cyclophosphamide/vincristine/procarbazine/prednisone) regimen and chemotherapy with ABVD (doxorubicin/bleomycin/vinblastine/dacarbazine) regimen.

Objectives

To determine the advantages and disadvantages of chemotherapy including escalated BEACOPP compared to chemotherapy including ABVD in the treatment of early unfavourable or advanced stage HL as first-line treatment.

Search methods

We searched for randomised controlled trials in MEDLINE, CENTRAL and conference proceedings (January 1985 to July 2013 and for the update to March 2017) and Embase (1985 to November 2008). Moreover we searched trial registries (March 2017; www.controlled-trials.com, www.clinicaltrialsregister.eu/ctr-search/search, clinicaltrials.gov, www.eortc.be, www.ghsg.org, www.ctc.usyd.edu.au, www.trialscentral.org/index.html)

Selection criteria

We included randomised controlled trials examining chemotherapy including at least two cycles of escalated BEACOPP regimens compared with chemotherapy including at least four cycles of ABVD regimens as first-line treatment for patients with early unfavourable stage or advanced stage HL.

Data collection and analysis

The effect measures we used were hazard ratios (HRs) for overall survival (OS), progression-free survival (PFS) and freedom from first progression.

We used risk ratios (RRs) relative risks to analyse harms: treatment-related mortality, secondary malignancies (including myeloid dysplastic syndrome (MDS) or acute myeloid leukaemia (AML)), infertility and adverse events.

Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma (Review)

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Quality of life was not reported in any trial, therefore not analysed. Two review authors independently extracted data and assessed quality of trials.

Main results

We screened 1796 records and identified five eligible trials in total i.e. one trial could be added on the previous review. These trials included only adults (16 to 65 years of age). We included all five trials with 3427 people in the meta-analyses: the HD9 and HD14 trials were co-ordinated in Germany, the HD2000 and GSM-HD trials were performed in Italy and the EORTC 20012 was conducted in Belgium. The overall risk of performance and detection bias was low for overall survival (OS), but was high for other outcomes, as therapy blinding was not feasible. The remaining 'Risk of bias' domains were low and unclear.

All trials reported results for OS and progression-free survival (PFS). In contrast to the our first published review (2011) the addition of results from the EORTC 20012 BEACOPP escalated increases OS (3142 participants; HR 0.74 (95% confidence interval (CI) 0.57 to 0.97; *high-quality evidence*). This means that only 90 (70 to 117) patients will die after five years in the BEACOPP escalated arm compared to 120 in the ABVD arm. This survival advantage is also reflected in an increased PFS with BEACOPP escalated (3142 participants; HR 0.54 (95% CI 0.45 to 0.64); *moderate-quality evidence*), meaning that after five years only 144 (121 to 168) patients will experience a progress, relapse or death in the BEACOPP escalated arm compared to 250 in the ABVD arm.

There is no evidence for a difference for treatment-related mortality (2700 participants, RR 2.15 (95% CI = 0.93 to 4.95), *low-quality evidence*).

Although the occurrence of MDS or AML may increase with BEACOPP escalated (3332 participants, RR 3.90 (95% CI 1.36 to 11.21); *low-quality evidence*), there is no evidence for a difference between both regimens for overall secondary malignancies (3332 participants, RR 1.00 (95% CI 0.68 to 1.48), *low-quality evidence*). However, the observation time of the studies included in the review is too short to be expected to demonstrate differences with respect to second solid tumours which would not be expected to show significance until around 15 years after treatment.

We are very uncertain how many female patients will be infertile due to chemotherapy and which arm might be favoured (106 participants, RR 1.37 (95% CI 0.83 to 2.26), *very low-quality evidence*). This is a very small sample, and the age of the patients was not detailed. No analysis of male fertility was provided.

Five trials reported adverse events and the analysis shows that the escalated BEACOPP regimens probably causes more haematological toxicities WHO grade III or IV ((anaemia: 2425 participants, RR 10.67 (95% CI 7.14 to 15.93); neutropenia: 519 participants, RR 1.80 (95% CI 1.52 to 2.13); thrombocytopenia: 2425 participants, RR 18.12 (95% CI 11.77 to 27.92); infections: 2425 participants, RR 3.73 (95% CI 2.58 to 5.38), all *low-quality evidence*).

Only one trial (EORTC 20012) planned to assess quality of life, however, no results were reported.

Authors' conclusions

This meta-analysis provides moderate- to *high-quality evidence* that adult patients between 16 and 60 years of age with early unfavourable and advanced stage HL benefit regarding OS and PFS from first-line chemotherapy including escalated BEACOPP. The proven benefit in OS for patients with advanced HL is a new finding of this updated review due to the inclusion of the results from the EORTC 20012 trial. Furthermore, there is only *low-quality evidence* of a difference in the total number of secondary malignancies, as the follow-up period might be too short to detect meaningful differences. *Low-quality evidence* also suggests that people treated with escalated BEACOPP may have a higher risk to develop secondary AML or MDS. Due to the availability of only *very low-quality evidence* available, we are unable to come to a conclusion in terms of infertility. This review does for the first time suggest a survival benefit. However, it is clear from this review that BEACOPP escalated may be more toxic than ABVD, and very important long-term side effects of second malignancies and infertility have not been sufficiently analysed yet.

PLAIN LANGUAGE SUMMARY

Comparison of the two international standards of chemotherapy for people with early unfavourable or advanced stage Hodgkin lymphoma

Review question

Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma (Review)

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For the treatment of early unfavourable and advanced stage Hodgkin lymphoma (HL) two different international standards are commonly used, either chemotherapy with escalated (intensified) BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) regimen or chemotherapy with ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) regimen.

Background

Hodgkin lymphoma is a malignancy of the lymphatic system. It is one of the most common cancers in young adults, particularly in their third decade of life, but it occurs also in children and elderly people. Within the last 50 years it has become one of the most curable forms of cancer. To find the best treatment with the greatest efficacy and least toxicity is the most important challenge in treating HL. There are two international standards for the treatment of early unfavourable or advanced stage HL: chemotherapy with escalated BEACOPP regimen initiated by the German Hodgkin Study Group (GHSG) and chemotherapy with ABVD regimen, which is widely used because it has been proven to be effective, well-tolerated and easy to administer. We aimed to clarify the advantages and disadvantages of both treatments by comparing the chance of survival (overall survival), the chance of recurrence of the tumour and the frequencies of adverse events after treatment in patients with early unfavourable stage or advanced stage HL.

Study characteristics

We found five eligible trials by the date of this updated review (search date March 2017). These trials included 3427 patients adult patients (16 to 65 years of age).

Key results

For this updated review there are new data available resulting in a benefit in terms of overall survival (OS) for people with early unfavourable and advanced HL receiving BEACOPP escalated for first-line treatment. Furthermore, the analysis shows a better chance of avoiding recurrence of the tumour in patients who received chemotherapy including BEACOPP escalated.

We analysed the following harms potentially caused by both regimens. There is no evidence for a difference for treatment-related mortality.

There is evidence for a higher risk of secondary acute myeloid leukaemia (AML) or myelodysplastic syndromes (MDS) in patients receiving BEACOPP escalated, but the total number of secondary malignancies does not show evidence for a difference between both treatment groups. However, the observation time of the studies included in the review is too short to be expected to demonstrate differences with respect to second solid tumours. We are very uncertain how many female patients will be infertile due to chemotherapy and which arm might be favoured, as the evaluated sample is very small. No data for male patients and risk for infertility was provided. Treatment with BEACOPP escalated caused a higher risk of adverse events such as anaemia, neutropenia, thrombocytopenia and infections.

Quality of life was not reported by any of the included trials. One trial stated it would assess quality of life, however, there were no results reported.

Quality of evidence

We assessed the quality of the evidence as high relating to overall survival, as moderate for progression-free survival and as low for secondary AML or MDS, secondary malignancies and treatment-related mortality and adverse events. The quality of evidence is very low for infertility.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Comparison of chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Patient or population: Patients with early unfavourable or advanced stage HL

Setting: Hospitals

Intervention: BEACOPP

Comparison: ABVD

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with ABVD	Risk with BEACOPP				
Mortality follow up: median 5 years	Study population ¹		HR 0.74 (0.57 to 0.97)	3142 (5 RCTs)	⊕⊕⊕⊕ HIGH	To provide correct results by using the GRADE software, we calculated mortality instead of overall survival
	120 per 1000	90 per 1000 (70 to 117)				
Progression, relapse or death follow up: median 5 years	Study population ³		HR 0.54 (0.45 to 0.64)	3142 (5 RCTs)	⊕⊕⊕○ MODERATE ³	To provide correct results by using the GRADE software, we calculated progression, relapse or death instead of progression-free survival
	250 per 1000	144 per 1000 (121 to 168)				
Adverse event: treatment-related mortality follow up median 5 years	Study population		RR 2.15 (0.93 to 4.95)	2700 (4 RCTs)	⊕⊕○○ LOW ⁴	
	5 per 1000	11 per 1000 (5 to 25)				
Adverse event: secondary malignancies follow up median 5 years	Study population		RR 1.00 (0.68 to 1.48)	3332 (5 RCTs)	⊕⊕○○ LOW ^{5,6}	

	29 per 1000	29 per 1000 (20 to 42)			
Adverse event: secondary malignancies: AML or MDS	Study population		RR 3.90 (1.36 to 11.21)	3332 (5 RCTs)	⊕⊕○○ LOW ⁴
	3 per 1000	10 per 1000 (3 to 29)			
Adverse event: infertility (secondary amenorrhoea)	Study population		RR 1.37 (0.83 to 2.26)	106 (1 RCT)	⊕○○○ VERY LOW ^{4,7}
follow up median 5 years	375 per 1000	514 per 1000 (311 to 847)			In the text referred to as infertility.
Quality of life					Not reported

* **The risk in the intervention group** (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

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

¹ we estimated the risk of mortality after 5 years in the ABVD arm as being 12%

² we estimated the risk of progress, relapse or mortality after 5 years in the ABVD arm as being 25%

³ one level down due to the open-label design of the included trials which could lead to performance or detection biases

⁴ two levels down due to very few events and wide confidence intervals (imprecision)

⁵ one level down due to few events and wide confidence intervals (imprecision)

⁶ one level down due to indirect results (follow-up period not long enough to detect meaningful differences)

⁷ one level down due to indirect results (secondary amenorrhoea measured instead of infertility) (indirectness)

BACKGROUND

Description of the condition

With an annual incidence of approximately two to three per 100,000 in Western countries, Hodgkin lymphoma (HL) is a comparatively rare disease (SEER 2012). However, it is one of the most common malignancies in young adults. In industrialised countries the age distribution of HL shows a first peak in the third decade and a second peak after the age of 55 (Swerdlow 2003; Thomas 2002).

Staging of HL is based on the Ann Arbor system (Carbone 1971), B symptoms and risk factors. Risk factors for HL are, for example, large mediastinal mass, three or more involved lymph node areas, high erythrocyte sedimentation rate (ESR), extranodal lesion, advanced age; and these may vary slightly between different study groups. Additionally, the definition of bulky disease (largest tumour diameter > 10 cm), often referred to as the Cotswold modification (Lister 1989), is taken into consideration. Generally, HL is classified into early favourable, early unfavourable and advanced stage (Engert 2007a; Klimm 2006). In Europe, the early favourable stage group usually comprises Ann Arbor stages I and II without risk factors. Early unfavourable stage includes those patients in stages I and IIA with risk factors, as well as selected patients with stage IIB disease. Most stage III and IV patients are classified in the advanced stage risk group (Diehl 2001; Engert 2003). Patients with Ann Arbor stage IIB and extranodal disease or bulky disease may be included in trials for advanced stages.

Standard chemotherapy for early unfavourable and advanced stage HL in the USA is ABVD, a combination of adriamycin, bleomycin, vinblastine and dacarbazine (Cheson 2004). The ABVD regimen has less severe toxic effects on bone marrow than the previously used MOPP regimen (mechlorethamine, vincristine, procarbazine, and prednisone) and a non-significant improvement in overall survival (OS) at five years compared to MOPP (66% for MOPP and 73% for ABVD) (Canellos 1992). The problem after both therapy regimens is that there is a 30% to 35% risk of disease progression or relapse within five years and a poor response to salvage treatment (Bonfante 1997; Josting 2002). The ABVD regimen has a number of advantages: it is all-intravenous, has less cumulative myelotoxicity, a lower risk of secondary malignancies and a lower rate of infertility compared with the previous regimen (Cheson 2004).

In Germany, the standard treatment for early unfavourable and advanced stage HL was COPP/ABVD until the middle 1990s. Then, based on a mathematical model of tumour growth and chemotherapy effects predicting that moderate dose escalation would increase tumour control by 10% to 15% at five years (Hasenclever 1996; Loeffler 1998), the German Hodgkin Study Group (GHSG) evaluated tolerability and efficacy of a new regimen, BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) in time and dose

intensification (Diehl 2003). After a median observation time of seven years, this study showed the superiority of the escalated BEACOPP regimen in comparison to COPP/ABVD in terms of freedom from treatment failure (85% versus 67%) and overall survival (90% versus 79%). However, an increased second leukaemia rate ((acute myeloid leukaemia (AML)/myeloid dysplastic syndrome (MDS)) was associated with the escalated BEACOPP regimen (Diehl 2003a; Diehl 2004).

Description of the intervention

This escalated BEACOPP schedule initiated by the GHSG in the late 1990s combines a shorter time (shorter cycle) and increased dose (increased single dose) scheme with the following substances: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone. The regimen should have been applied in an escalated dose, which is given in the Additional tables, Table 1 (Diehl 2003) and a cycle should have been repeated after 21 days. As supportive therapy, granulocyte-colony stimulating factor (G-CSF) should have been administered during the escalated BEACOPP regimen from day eight of the cycle (Additional tables, Table 1).

We considered treatment with chemotherapy including ABVD regimen with or without radiotherapy as control condition. The ABVD regimen includes the following drugs: doxorubicin (adriamycin), bleomycin, vinblastine, and dacarbazine. A cycle should have been repeated after 28 days. The chemotherapy of the comparator arm should have included at least four cycles of ABVD.

If additional radiotherapy was applied, the condition (based on remission status), dosage as well as field (involved or extended) must have been the same in both control and intervention arms. Supportive care should have been similar between control and intervention arms.

How the intervention might work

For people with early unfavourable HL, the investigation of more intensive chemotherapy regimens is an approach to improve long-term results. The GHSG recommends to treat people with early unfavourable stages with four cycles of chemotherapy (e.g. two cycles escalated BEACOPP followed by two cycles ABVD). People in advanced stages should receive four to six cycles of escalated BEACOPP followed by two to four cycles of standard BEACOPP. The ABVD regimen is considered as standard therapy for people with HL in some study groups (e.g. the Southwest Oncology Group considered in the trial E2496 eight cycles of ABVD as standard therapy). This regimen is widely used because it is well-proven, supported by phase III data from the 1990s and it is well-tolerated and easy to administer. It is effective for patients with early unfavourable or advanced stage without inducing too many adverse events (Gobbi 2005).

Why it is important to do this review

The most important challenge in treating HL is to find the optimal treatment that accomplishes the best efficacy with least toxicity (Connors 2001; Connors 2005a). So far there are two different standards for the treatment of early unfavourable staged and advanced staged HL. Chemotherapy with the ABVD regimen is widely used in North America (Canellos 2005a), while chemotherapy with escalated BEACOPP regimen is mostly used in Germany and some other parts of Europe.

OBJECTIVES

To determine the advantages and disadvantages of chemotherapy including escalated BEACOPP compared to chemotherapy including ABVD in the treatment of early unfavourable or advanced stage Hodgkin lymphoma (HL).

METHODS

Criteria for considering studies for this review

Types of studies

We considered only randomised controlled trials (RCT) as primary studies in this review and meta-analysis (O'Connor 2011). We included both full text and abstract publications.

Types of participants

We included studies on male and female patients with previously untreated and histologically-confirmed diagnosis of early unfavourable or advanced stage Hodgkin lymphoma (HL). We would have accepted trials with protocols for children as well as adults, but we could not identify any randomised trials including children.

If the trial population had been mixed, including participants with haematological malignancies, we would have used data from the HL subgroup. If subgroups had been available (not reported and not provided after personally contacting the author), we would have included only trials with a minimum of 80% of patients with HL, but we could not identify any trial of this type.

We included trials for early unfavourable or advanced stage HL. We considered patients with Ann Arbor stage I/II with risk factors as early unfavourable and patients with Ann Arbor stage III/IV independently from risk factors as advanced stages. We accepted the risk factors used by the respective study group or institution and kept the classification defined and used by the respective study group or institution.

Types of interventions

To assure equal doses of chemotherapy, we considered chemotherapy including at least two cycles of escalated BEACOPP as the intervention condition, and regimens including at least four cycles of ABVD as the control condition, both with or without radiotherapy as first-line treatment for early unfavourable or advanced stage HL (Hasenclever 2001).

We did not consider chemotherapy with BEACOPP given in the standard dose in this systematic review because the GHSG HD9 trial showed clearly better progression-free survival (PFS) results with the escalated regimen (Diehl 2004).

If additional radiotherapy was applied, the condition, dosage and field should have been the same in both control and intervention arms.

Types of outcome measures

Primary outcomes

As primary outcomes we chose overall survival (OS) and progression-free survival (PFS). The definition of OS was time from randomisation until death as a result of any cause (Cheson 2007a). PFS was defined as the time from randomisation until disease progression, relapse or death as a result of any cause. PFS was provided by GHSG HD14, HD 2000 and EORTC 20012. However, we also accepted other definitions that addressed progression in the process of the disease such as freedom from treatment failure (FFTF) and event-free survival (EFS). Freedom from treatment failure was defined as the time from randomisation until progression during treatment, lack of complete response at the end of treatment, relapse and death from any cause (GHSG HD9). The definition of EFS was time from randomisation to evidence of severe toxicity causing definite treatment discontinuation, progressive lymphoma, cardiorespiratory failure, secondary leukaemia, death due to any cause, whichever occurred first (GSM-HD 2008). Within the review, data coming under these definitions were discussed as results of PFS.

Secondary outcomes

In the previous version of this review the authors selected complete response (CR) rate as a secondary outcome because the endpoint is directly measuring the response to the therapy and is one of the outcomes often evaluated in clinical trials in oncology. The review authors also analysed other tumour control outcomes such as freedom from first progression defined as time from randomisation to first evidence of progressive lymphoma (GSM-HD 2008). In this updated version, we considered these endpoints as less patient-relevant ones, therefore, we did not present the results for these outcomes in the [Summary of findings for the main comparison](#). Other secondary outcomes were harms. We evaluated the following parameters for this purpose:

- treatment-related mortality;
- secondary malignancies, particularly myeloid dysplastic syndrome (MDS) and acute myeloid leukaemia (AML);
- infertility (since infertility is only measurable indirectly, all assessed outcomes with respect to infertility are reported in the review);
- adverse events: haematological grade III or IV toxicity, assessed according to the WHO-scale, particularly thrombocytopenia, leucopenia, anaemia and infection;
- adverse events: cardiopulmonary toxicity: pulmonary toxicity (bleomycin-induced lung fibrosis).

We additionally assessed quality of life in this updated review.

Search methods for identification of studies

We adapted search strategies from those suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2008). We applied no language restriction to reduce the language bias.

Electronic searches

For the primary review published in 2011 we searched the following databases in two steps:

First step: MEDLINE (1985 to November 2008, search strategy see [Appendix 1](#)), Embase (1985 to November 2008, search strategy see [Appendix 2](#)) and Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library 2008, Issue 3, search strategy see [Appendix 3](#)).

Second step: In 2010 we adapted the search strategies and performed another search in MEDLINE (November 2008 to August 2010, search strategy see [Appendix 4](#)) and CENTRAL (the Cochrane Library 2010 issue 8, search strategy see [Appendix 5](#)). The Embase search was not updated because our account for this database ended in the meantime.

To keep the review up to date we used the adapted search strategies and performed another search in MEDLINE (August 2010 to March 2017, search strategy see [Appendix 6](#)) and CENTRAL (the Cochrane Library 2017 issue 03, search strategy see [Appendix 7](#)).

Searching other resources

For the primary review, we conducted the search for the years 1990 until August 2010. We searched those years which were included in CENTRAL via CENTRAL. For the updated review we searched the conference proceedings of annual meetings of the following societies for abstracts:

- American Society of Clinical Oncology (ASCO) (up to the issue of 2016);
- American Society of Hematology (ASH) (up to the issue of 2016);
- European Hematology Association (EHA) (up to the issue of 2016);

- International Symposium on Hodgkin Lymphoma (ISHL) (up to the issue of 2016).

Moreover, we tried to identify trials with the following methods.

- Handsearching of references
 - Citations from identified trials and relevant review articles.
- We checked references of all identified trials, relevant review articles and current treatment guidelines for further literature.
- Personal contacts
 - We contacted experts in the field in order to locate other trials.
- Databases of ongoing trials:
 - Meta-register of controlled trials: <http://www.controlled-trials.com/mrct/>
- We also searched a number of databases and websites of relevant institutions, agencies, organisations (e.g. study groups), societies and registries for (ongoing) trials (August 2016):

- Register of controlled trials: www.controlled-trials.com
- EU clinical trials register: www.clinicaltrialsregister.eu/ctr-search/search
- Clinicaltrials.gov: clinicaltrials.gov
- www.eortc.be
- www.ghsg.org
- www.ctc.usyd.edu.au
- www.trialscentral.org/index.html

Data collection and analysis

Selection of studies

Two review authors (AW, NS) independently screened titles and abstracts of studies identified from the sources listed above for potentially relevant studies. First, we screened and discarded studies that were clearly ineligible. We assessed selected studies with an eligibility form to determine whether they met the inclusion criteria. We resolved any disagreement between the two review authors by discussion. We would have sought further information from the authors, whose articles contained insufficient data to make a decision about eligibility. The eligibility form contained the following questions.

- Is the study described as a randomised trial for patients?
- Were the participants newly diagnosed with early unfavourable or advanced stage Hodgkin lymphoma?
- Were the participants in the intervention group treated with at least two cycles of escalated BEACOPP?
- Were the participants in the control group treated with at least four cycles of ABVD?

To be eligible, studies had to meet all of the criteria stated above. We also identified duplicate reports.

We obtained all full-text versions of all eligible studies for quality assessment and data collection. At every stage of searching and screening of the literature, we documented the overall number of studies identified, excluded and included with reasons in a flow diagram (Moher 2009). We resolved disagreements arising at any stage by discussion and consensus. If an agreement had not been reached, we would have asked a third review author (content expert) to give his or her opinion, in accordance with Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), but this procedure was not necessary.

Data extraction and management

We used both full-text versions and abstracts (if full-text was not published) of eligible studies to retrieve the data. In case these did not provide sufficient information, we contacted authors of individual studies for additional details (e.g. HD 2000; GHSG HD9; GHSG HD14). We conducted data extraction according to the guidelines proposed by Cochrane. For this review, two review authors (AW, NS) extracted data independently from the studies using a standardised data extraction form containing the following items.

- **General information:** first author of the publication, title of study, study ID, author's contact address (if available), source, publication date, country, language.
- **Quality and 'Risk of bias' assessment:** sequence generation, allocation concealment, blinding (participants, personnel, outcome assessors), incomplete outcome data, selective outcome reporting, other sources of bias.
 - **Trial details:** trial design, objectives of the trial, types of outcomes reported, location, setting, sample size calculation, randomisation, treatment allocation, inclusion/exclusion criteria, reasons for exclusion, comparability of groups, length of follow-up, stratification, stopping rules described, statistical analysis, results, power calculation, recruitment period, funding.
 - **Characteristics of participants:** age, gender, ethnicity, total number recruited/randomised/analysed (total and for each arm), stage of the disease (Ann Arbor stage, B-symptoms and risk factors), tumour response (if it was a criteria for randomisation), lost to follow-up, dropouts by trial arm and reasons.
 - **Interventions:** type of chemotherapy (name, dose and frequency of drugs from the chemotherapy regimen), number of cycles, length of a cycle and route of interventions, compliance to interventions, supportive therapy given, failure to maintain dose intensity, protocol violations, additional radiotherapy (dosage, field).
 - **Outcomes measured:** overall survival (OS), progression-free survival (PFS) or similar tumour control outcomes, treatment-related mortality, secondary neoplasms (including overall secondary malignancies and AML and MDS), infertility, adverse events, especially haematological toxicity, cardiopulmonary

toxicity, quality of life, response rate, freedom from treatment failure (FFTF), number of patients evaluated for each outcome, length of follow-up for survival outcomes and definitions of the outcomes.

We extracted trials reported in more than one publication on one form only. We resolved potential disagreements by consensus. If an agreement had not been reached, we would have asked a third review author (content expert) to give his or her opinion, but this procedure was not necessary.

Assessment of risk of bias in included studies

Two review authors (AW, NS) assessed eligible studies obtained in the process of study selection as described above for methodological quality. To assess quality, we used the Cochrane 'Risk of bias' table. To improve transparency of judgements, we included quotations from the full-text article or from supplemental information from the author in the notes section of the 'Risk of bias' table.

We included the following items in the 'Risk of bias' assessment for randomised trials. For details of bias assessment we referred to Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a).

There are three categories: yes (low risk of bias), unclear, and no (high risk of bias) in response to the following questions.

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

Measures of treatment effect

For binary variables, we estimated treatment effect measures of individual studies as relative effect measures risk ratio (RR) with corresponding 95% confidence intervals by using the Mantel-Haenszel method in a fixed-effect model. For time-to-event variables, we estimated treatment effects as hazard ratio (HR) with corresponding 95% confidence intervals by using the generic inverse variance method in a fixed-effect model. For each trial, we extracted information about time-to-event outcome using the methods described by Tierney (Parmar 1998; Tierney 2007).

Dealing with missing data

We dealt with missing data as suggested in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). We contacted the original investigators to request missing data and received additional information from Mournier and colleagues. We performed sensitivity analysis to assess how sensitive results were to reasonable changes in the assumptions that had

been made. We addressed the potential impact of missing data on the findings of the review in the discussion.

Assessment of heterogeneity

We assessed heterogeneity of treatment effects between trials by using a Chi^2 test with a significance level at $P < 0.1$. We used the I^2 statistic to quantify possible heterogeneity ($30\% < I^2 < 75\%$: moderate heterogeneity, $75\% < I^2$: considerable heterogeneity) (Deeks 2011).

We explored potential causes of heterogeneity by performing sensitivity and subgroup analysis.

Assessment of reporting biases

In a meta-analysis with more than 10 trials, we would have explored potential reporting bias by generating a funnel plot and statistically testing this by conducting a linear regression test (Sterne 2011). A P value less than 0.1 would have been considered significant for this test. However, we only included five trials so this test was not done.

Data synthesis

According to the recommendations of Cochrane (Deeks 2011), we performed meta-analyses by using a fixed-effect model (i.e. generic inverse variance method for time-to-event outcomes and a Mantel-Haenszel method for dichotomous outcomes).

We performed analyses according to the recommendations of Cochrane using the Review Manager (Review Manager 5.3) and listed the predefined outcomes OS, PFS, the adverse events treatment-related mortality, secondary malignancies, secondary AML/MDS, and infertility, and quality of life in a 'Summary of findings' table [Summary of findings for the main comparison](#) on absolute risks in each group with the help of [GRADE pro 2014](#).

Subgroup analysis and investigation of heterogeneity

We planned to take the following parameters into consideration for subgroup analysis of the primary outcomes:

- stage of the disease (early unfavourable versus advanced);
- age (e.g. children versus adults ≤ 50 years versus adults > 50 years, or depending on the median age of the trial);
- treatment regimens (i.e. only ABVD regimen versus chemotherapy including ABVD regimen);
- length of therapy (e.g. four versus eight cycles of chemotherapy);

- number of cycles of escalated BEACOPP (i.e. two versus four versus eight);
- radiotherapy (with or without radiotherapy);
- sequence (e.g. BEACOPP followed by other agents versus other chemotherapeutic agents followed by BEACOPP);
- length of follow-up (i.e. long follow-up (more than five years) versus short follow-up (five years or less);
- same total number of cycles of chemotherapy for the control and intervention groups (yes versus no).

We did not conduct planned subgroup analysis by "age", "length of therapy", "sequence", and "total number of cycles of chemotherapy" because the included studies were similar with regard to these characteristics.

We did a test for subgroup differences and considered a P-value of less than 0.05 as statistical significant for all the outcomes mentioned in the 'Summary of findings' table.

Sensitivity analysis

We would have assessed robustness of the results of the primary outcomes by analyses of the kind of publication (full-text publications/abstracts) and the type of results (preliminary results/mature results). However, all included trials have been published as full texts.

RESULTS

Description of studies

Results of the search

In total, we screened 790 for the primary review and for the updated version 1006 potentially relevant records up to March 2017 (1796 references after duplicates removed). Of these, 1706 were excluded at the initial stage of screening because they did not fulfil our predefined inclusion criteria. The remaining 90 publications were retrieved as full-text publications or abstract publications for detailed evaluation. Of these 90 references, 37 were excluded. Five eligible trials (all published) were identified and finally all five trials (53 publications) with 3427 patients were formally included in the main analyses of this review (see [Figure 1](#)).

Figure 1. Study flow diagram.

Included studies

Five trials ([EORTC 20012](#); [GHSG HD9](#); [GHSG HD14](#); [GSM-HD 2008](#); [HD 2000](#)) were included in the review. We extracted data from full-text publications for all five trials. Furthermore, we received additional information from Gianni and colleagues and Borchmann and colleagues to complete the outcome data as well as additional information of patient characteristics of the published abstracts.

See also the table [Characteristics of included studies](#).

Design

Of the five included trials, three trials were two-armed randomised controlled trials ([EORTC 20012](#); [GHSG HD14](#); [GSM-HD 2008](#)) and two trials were three-armed randomised controlled trials ([GHSG HD9](#); [HD 2000](#)). One of these trials recruited patients from 1993 to 1998 ([GHSG HD9](#)), and the others within a period between 2000 to 2008.

Participants

A total of 4124 patients with newly confirmed diagnosis of early unfavourable ([GHSG HD14](#) N = 1655) or advanced stage HL ([EORTC 20012](#) N = 549; [GHSG HD9](#) N = 1282; [GSM-HD 2008](#) N = 331; [HD 2000](#) N = 307) were randomised within the five trials, but only 3427 of these could be included in this review as they received regimens including escalated BEACOPP or ABVD ([EORTC 20012](#) N = 549; [GHSG HD9](#) N = 727; [GHSG HD14](#) N = 1623; [GSM-HD 2008](#) N = 3142; [HD 2000](#) N = 197).

All five studies had different eligibility criteria for age ([EORTC 20012](#): 16 to 60 years [GHSG HD9](#): 16 to 65 years; [GHSG HD14](#): 16 to 60 years; [GSM-HD 2008](#): up to 60 years of age; [HD 2000](#): older than 16 years of age. Only three trials reported data regarding the median age of included patients in these studies ([EORTC 20012](#): 35.2 years; [GHSG HD9](#): 32 years; [HD 2000](#): 29 years). The proportion of the patients being older than 45 or 50 years was between 15% to 26% in the three reporting trials ([GHSG HD9](#): escalated BEACOPP: 15% of 466 patients 50 to 65 years old; standard BEACOPP: 18% of 469 patients 50 to 65 years old; COPP/ABVD: 16% of 260 patients 50 to 65 years old; [GSM-HD 2008](#): escalated BEACOPP 20% of 155 patients at least 45 years; ABVD 23% of 166 patients at least 45 years); [HD 2000](#): escalated BEACOPP: 17% of 98 patients at least 45 years; CEC: 26% of 98 patients at least 45 years; ABVD: 18% of 99 patients at least 45 years.

Location

The included trials were co-ordinated from Europe. Two were performed by the German Hodgkin Study Group ([GHSG HD9](#); [GHSG HD14](#)), two others were provided by Italian study groups ([GSM-HD 2008](#); [HD 2000](#)), the [EORTC 20012](#) trial had its headquarter in Belgium.

Intervention

Patients from the included trials were either treated with chemotherapy including escalated BEACOPP or with chemotherapy including ABVD as primary treatment for HL. The included trials used the following regimens: four escalated plus two standard courses of BEACOPP versus six courses of ABVD versus six courses of CEC (cyclophosphamide, lomustine, vindesine, melphalan, prednisone, epidoxorubicin, vincristine, procarbazine, vinblastine, and bleomycin) ([HD 2000](#)); two escalated courses of BEACOPP plus two courses of ABVD versus four courses of ABVD ([GHSG HD14](#)), eight escalated courses of BEACOPP versus eight courses of cyclophosphamide, vincristine, procarbazine, and prednisone (COPP) alternating with ABVD ([GHSG HD9](#)), four escalated plus four standard courses of BEACOPP versus six to eight courses of ABVD [EORTC 20012](#) and [GSM-HD 2008](#). Three of these trials scheduled radiotherapy after chemotherapy for sites of previous bulky disease and slowly or partially responding sites with 30 to 40 Gray ([GHSG HD9](#); [GSM-HD 2008](#); [HD 2000](#)). In the [GHSG HD14](#) trial, all patients received involved-field radiotherapy of 30 Gray. In the [EORTC 20012](#) trial, none of the patients had received radiotherapy.

Outcomes

Primary outcome measure

All included trials analysed overall survival (OS). The median observation times for OS were as follows: 10 years for two trials ([GHSG HD9](#); [HD 2000](#)), however, as no hazard ratios (HRs) were provided for [HD 2000](#), only the short-term data could be analysed. The median observation time was six years for one trial ([GSM-HD 2008](#)); three to 3.5 years for two trials ([EORTC 20012](#); [GHSG HD14](#)). Progression-free survival (PFS) or similar outcomes (for further information see "Types of outcome measures, Primary outcomes") were analysed by all included trials. The median observation times for these outcomes were the same as for OS.

Secondary outcome measures

Four trials ([EORTC 20012](#); [GHSG HD9](#); [GSM-HD 2008](#); [HD 2000](#)) reported complete response (CR) rates. Analysable information with regard to adverse events was reported by the following studies: haematological grade III or IV toxicity by three studies ([GHSG HD9](#); [GHSG HD14](#); [HD 2000](#)), secondary malignancies by three studies ([GHSG HD9](#); [GHSG HD14](#); [HD 2000](#)), treatment-related mortality was reported by one study ([HD 2000](#)), and respiratory toxicity by one study ([GHSG HD9](#)). Time to progression was reported by one study ([GSM-HD 2008](#)) and data regarding infertility was reported only by one study ([GHSG HD9](#)).

Excluded studies

A total of 37 articles were excluded after detailed evaluation of full-text publications. The main reasons for exclusion were:

- 24 non-randomised comparisons or reviews;
- 14 did not evaluate escalated BEACOPP versus ABVD.

These publications are described under [Characteristics of excluded studies](#).

Ongoing studies

The only ongoing study noticed in the primary review, [EORTC 20012](#), has been published and included in this review. We could not identify any further ongoing trial addressing the objective of this review.

Risk of bias in included studies

Further details on the 'Risk of bias' assessment are shown in Figure 2 and [Figure 2](#).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias): Overall survival	Blinding (performance bias and detection bias): Other outcomes	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
EORTC 20012	+	+	+	-	+	-	?
GHSG HD14	?	?	+	-	+	?	?
GHSG HD9	+	+	+	-	+	?	?
GSM-HD 2008	?	?	+	-	+	+	?
HD 2000	?	?	+	-	+	?	?

Allocation

The [GHSG HD9](#) and [EORTC 20012](#) trials reported that treatment allocation of patients was performed at a central trials office and sequence was generated by computer (low risk of bias). The other trials did not state any information with respect to these issues, therefore we judged as unclear risk of bias.

Blinding

None of the trials reported information about blinding. Results with respect to OS are judged not to be influenced by this source of bias, because to define the status of a patient as dead or alive is not a question of individual judgement. With regard to the remaining outcomes all trials were judged “high” for the question of blinding, as it is known that blinding is not feasible in this setting and might influence the outcomes.

Incomplete outcome data

[HD 2000](#), [GHSG HD9](#) and [GHSG HD14](#) described missing outcome data in detail. The [GHSG HD9](#) trial excluded 80 patients because they did not fulfil the inclusion criteria of the study and five patients due to other reasons. [HD 2000](#) excluded all in all eight patients. Missing outcome data in both trials were balanced in numbers across intervention groups (see ‘Risk of bias’ tables for further details). [GHSG HD14](#) did not include 32 of 1655 patients in the analyses, but missing outcome data were balanced in numbers across both groups (see ‘Risk of bias’ tables for further details). [GSM-HD 2008](#) and [EORTC 20012](#) analysed all randomised patients. However, due to the small proportion of missing data in most trials and the detailed descriptions in two of them, we do not believe that bias was introduced into the meta-analysis by missing data. Therefore we judged attrition bias “low” for all studies.

Selective reporting

As all the outcomes are reported for the [GSM-HD 2008](#) trials as published in the protocol, we judge the risk of bias as low. [HD 2000](#) is registered in a clinical study registry, but no outcomes are reported, therefore we judge the potential risk of bias as unclear. We could not identify protocols for [GHSG HD14](#) and [GHSG HD9](#) and judge the risk of bias as being unclear. In the study registry it is mentioned that [EORTC 20012](#) evaluated quality of life, but this outcome is not published, therefore we judge potential risk of bias as high.

Other potential sources of bias

In the [GHSG HD9](#) trial, randomisation to the escalated BEACOPP arm started later than the randomisation to the ABVD arm and the standard BEACOPP arm. Furthermore, randomisation to the COPP/ABVD arm was stopped after the first interim analysis due to the fact that both BEACOPP groups together were significantly superior to COPP/ABVD in terms of the rate of freedom from treatment failure (FFTF) ([Diehl 2003](#)). According to this potential risk of bias, the analyses of OS and PFS were based on data of patients recruited within the same time period. J. Franklin, statistician for the HD9 trial, recalculated HRs with confidence intervals (CI) for OS and PFS by considering only patients who were randomised in the same time-period (between date 1 and date 2). He had a direct access to the individual patient data. It means he considered 265 patients for the escalated BEACOPP arm and 177 patients for the COPP/ABVD arm. We generally judged the risk of other potential sources as “unclear”.

The [HD 2000](#) trial was initially designed to examine the myelotoxicity of CEC and BEACOPP regimens compared to ABVD, but the protocol was amended after the first 18 months to test the effect of BEACOPP regimen versus ABVD and CEC, respectively. To calculate the power of the study a one-sided test was used to consider the expected superiority of BEACOPP in terms of failure-free survival (FFS). To use a one-sided test might have led to an underpowered design of the study which leads to an estimate of “high” risk.

Effects of interventions

See: [Summary of findings for the main comparison Escalated BEACOPP versus chemotherapy including ABVD](#)

Primary outcome: overall survival (OS)

Participants

All five trials provided information regarding this outcome. To avoid the introduction of potential risk of bias that might have been caused by the [GHSG HD9](#) trial, patients of this trial had to be recruited in a parallel time period to be considered in the analyses ([Other potential sources of bias](#)). Together with the patients randomised in the four other trials, this analysis included 3142 participants.

Results

In the main analysis, there was a statistically significant difference between treatment with escalated BEACOPP or ABVD on OS favouring BEACOPP: hazard ratio (HR) 0.74 (95% confidence interval (CI) 0.57 to 0.97, $P = 0.03$). There was no statistical heterogeneity between the trials, with an $I^2 = 0\%$ (see [Figure 3](#)).

Figure 3. Forest plot of comparison: 1 Analysis of Overall Survival, outcome: 1.1 OS - all - same recruitment period between the 2 arms (HD9).

Subgroup analysis

We conducted subgroup analysis to explore the underlying clinical heterogeneity in order to assess the influence of clinical differences between the studies.

The “test for subgroup differences” showed no statistical differences between the following subgroups:

- different stages of disease ($P = 0.28$, early unfavourable: one trial, $N = 1623$; advanced: four trials, $N = 1519$); [Analysis 1.2](#)
- different types of treatment regimens ($P = 0.29$, only ABVD: four trials, $N = 2700$; ABVD including regimen: one trial, $N = 442$); [Analysis 1.3](#)
- different numbers of cycles of escalated BEACOPP ($P = 0.43$, eight cycles: one trial, $N = 442$; four cycles: three trials, $N = 1077$; two cycles: one trial, $N = 1623$); [Analysis 1.4](#)
- different length of follow-up ($P = 0.29$, short-term follow-up: four trials, $N = 2700$, long-term follow-up: one trial, $N = 442$); [Analysis 1.5](#)
- radiotherapy: ($P = 0.84$, without radiotherapy: one trial, $N = 549$; with radiotherapy: four trials, $N = 2583$); [Analysis 1.6](#).

Subgroup analyses in terms of “age”, “length of therapy”, “sequence”, and “same total number of cycles of chemotherapy” were not performed, because the identified studies showed no differ-

ences due to these study characteristics (see [Subgroup analysis and investigation of heterogeneity](#)).

Sensitivity analysis

We also performed a sensitivity analysis for all recruited patients with potential risk of bias due to different time periods of recruitment in [GHSG HD9](#). This analysis showed also statistically significant effect favouring BEACOPP escalated (HR 0.66, 95% CI 0.52 to 0.84, $N = 3427$); [Analysis 1.7](#).

Primary outcome: progression-free survival

Participants

All five trials provided information regarding this outcome. Similar to the procedure for participants of OS, we used the data of patients who were recruited in the [GHSG HD9](#) trial in parallel with the other three trials to perform the main analysis of PFS. This was to avoid the introduction of potential risk of bias ([Other potential sources of bias](#)). This analyses included data of 3142 patients from all five studies.

Results

The main analysis of PFS showed a statistically significant improved outcome for patients with escalated BEACOPP: HR was 0.54 (95% CI 0.45 to 0.64), see [Figure 4](#). There was no heterogeneity between trials ($I^2 = 0\%$).

Figure 4. Forest plot of comparison: 2 Analysis of Progression Free Survival, outcome: 2.1 PFS - all - same recruitment period between the 2 arms (HD9).

Subgroup analysis

We conducted subgroup analysis to explore the potential underlying clinical heterogeneity between the studies. The “test for subgroup differences” showed no statistical differences between the following subgroups:

- different stages of disease ($P = 0.47$, early unfavourable: one trial, $N = 1623$; advanced: four trials, $N = 1519$); [Analysis 2.2](#)
- different types of treatment regimens ($P = 0.62$, only ABVD: four trials, $N = 2700$; ABVD including regimen: one trial, $N = 442$); [Analysis 2.3](#)
- different numbers of cycles of escalated BEACOPP ($P = 0.61$, eight cycles: one trial, $N = 442$; four cycles: three trials, $N = 1077$; two cycles: one trial, $N = 1623$); [Analysis 2.4](#)
- different length of follow-up ($P = 0.62$, short-term follow-up: four trials, $N = 2700$; long-term follow-up: one trial, $N = 442$); [Analysis 2.5](#)
- radiotherapy: ($P = 0.69$, without radiotherapy: one trial, $N = 549$; with radiotherapy: four trials, $N = 2593$); [Analysis 2.6](#).

As explained above, subgroup analyses in terms of “age”, “length of therapy”, “sequence”, and “same total number of cycles of chemotherapy” were not performed (see [Subgroup analysis and investigation of heterogeneity](#)).

Sensitivity analysis

We also performed a sensitivity analysis for all recruited patients with potential risk of bias due to different time periods of recruitment in [GHSG HD9](#). This analysis showed also statistically significant effect favouring BEACOPP escalated ($HR 0.51$, 95% CI 0.43 to 0.60, $N = 3427$); [Analysis 2.7](#).

Secondary outcome: treatment-related mortality

Participants

Data of the treatment-related mortality was available from the four trials [EORTC 20012 HD 2000](#), [GSM-HD 2008](#) and [GHSG HD14](#) including 2700 participants.

Results

Escalated BEACOPP showed no clear evidence for a difference in terms of treatment-related mortality, but might be increased with BEACOPP escalated (four trials, $N = 2700$, (risk ratio (RR) 2.15, 95% CI 0.93 to 4.95) as shown in [Analysis 3.1](#)

We conducted subgroup analysis to explore the potential underlying clinical heterogeneity between the studies. The “test for subgroup differences” showed no statistical differences between the following subgroups:

- different stages of disease ($P = 0.28$, early unfavourable: one trial, $N = 1623$; advanced: three trials, $N = 1077$); [Analysis 3.2](#)
- different numbers of cycles of escalated BEACOPP ($P = 0.28$, early unfavourable: one trial, $N = 1623$; advanced: three trials, $N = 1077$); [Analysis 3.3](#)

The subgroup analysis for addition of radiotherapy showed a statistical significant subgroup difference ($P = 0.04$). We did not find evidence for a difference between both intervention arms, if no radiotherapy was applied (RR 0.84, 95% CI 0.26 to 2.71, one trial), but an advantage for the ABVD arm, if additional radiotherapy

was administered (RR 6.13, 95% CI 1.38 to 27.26, three trials); [Analysis 3.4](#). However, due to the low number of events results needs to be confirmed before final conclusions can be drawn.

Secondary outcome: secondary malignancies

Participants

The number of secondary malignancies was reported by all trials ([EORTC 20012](#); [GHSG HD9](#); [GHSG HD14](#); [HD 2000](#); [GSM-HD 2008](#)), including 3332 patients.

Results

There was no evidence for a difference between both regimens in terms of total rate of secondary malignancies (five trials, $N = 3332$, RR 1.00, 95% CI 0.68 to 1.48, $P = 0.92$); [Analysis 4.1](#)

The “test for subgroup differences” showed no statistical differences between the following subgroups: different stages of disease, different types of treatment regimens, different numbers of cycles of escalated BEACOPP, different length of follow-up and whether additional radiotherapy was applied (see [Analysis 4.2](#); [Analysis 4.3](#); [Analysis 4.4](#); [Analysis 4.5](#); [Analysis 4.6](#)).

Secondary outcome: secondary AML or MDS

Participants

All trials ([EORTC 20012](#); [GHSG HD14](#); [GHSG HD9](#); [GSM-HD 2008](#); [HD 2000](#)) reported occurrence of MDS or AML, $N = 3332$.

Results

There was a statistically significantly increased occurrence of MDS or AML in BEACOPP included regimens (five trials, $N = 3332$, RR 3.90, 95% CI 1.36 to 11.21, $P = 0.02$); [Analysis 5.1](#)

We did not identify any statistical differences between the following subgroups: different stages of disease, different types of treatment regimens, different numbers of cycles of escalated BEACOPP, different length of follow-up and whether additional radiotherapy was applied (see [Analysis 5.2](#); [Analysis 5.3](#); [Analysis 5.4](#); [Analysis 5.5](#); [Analysis 5.6](#)).

Secondary outcome: infertility

Data regarding infertility were only applied for 106 women of the [GHSG HD9](#) trial.

Results

Secondary amenorrhoea was evaluated as a quantity of infertility, without evidence for a difference between both arms (one trial, $N = 106$, RR 1.37 0.83 to 2.26, $P = 0.22$); [Analysis 6.1](#)

As only one trial was included, subgroup analyses were not possible

Secondary outcome: adverse events

Participants

Data for the majority of acute adverse effects WHO grade III or IV (i.e. anaemia, infection, thrombocytopenia, mucositis, nausea/vomiting, neurologic toxicity, leucopenia, alopecia, pain) were reported by three trials ([GHSG HD14](#); [GHSG HD9](#); [HD 2000](#)) including 2425 participants. Respiratory adverse events were reported by the [GHSG HD14](#), [GHSG HD9](#) and [GSM-HD 2008](#) trial. The following adverse events were reported by two trials each: neutropenia ([GSM-HD 2008](#); [HD 2000](#); $N = 519$), constipation ([GHSG HD9](#); [HD 2000](#); $N = 923$), analysis of skin

(GHSG HD14; GHSG HD9; N = 2227) and heart (GHSG HD14; GSM-HD 2008; N = 1823),

Due to the low number of included trials we did not perform subgroup analyses.

Results

The escalated BEACOPP regimen caused statistically significantly more acute adverse effects WHO grade III or IV in terms of:

- anaemia (three trials, N = 2425, RR 10.67, 95% CI 7.14 to 15.93, $P < 0.00001$); [Analysis 7.1](#)
- infection (three trials, N = 2425, RR 3.73, 95% CI 2.58 to 5.38, $P < 0.00001$); [Analysis 8.1](#)
- neutropenia (two trials, N = 519, RR 1.80, 95% CI 1.52 to 2.13, $P < 0.00001$); [Analysis 9.1](#)
- thrombocytopenia (three trials, N = 2425, RR 18.12, 95% CI 11.77 to 27.92, $P < 0.00001$); [Analysis 10.1](#)
- alopecia (three trials, N = 2425, RR 1.98 95% CI 1.78 to 2.21, $P < 0.00001$); [Analysis 11.1](#)
- mucositis (three trials, N = 2425, RR 8.04, 95% CI 3.72 to 17.38, $P = 0.0005$); [Analysis 13.1](#)
- neurologic toxicity (three trials, N = 2425, RR 2.04, 95% CI 1.19 to 3.50, $P = 0.009$); [Analysis 15.1](#)
- acute adverse effect of the respiratory tract (three trials, N = 2549, RR 1.80, 95% CI 1.01 to 3.20, $P = 0.05$); [Analysis 17.1](#)
- pain (three trials, N = 2425, RR 2.62, 95% CI 1.76 to 3.90, $P < 0.00001$); [Analysis 16.1](#)

No statistically significant differences between escalated BEACOPP and ABVD-like regimens were found for:

- constipation (two trials, N = 923, RR 1.19, 95% CI 0.56 to 2.55, $P = 0.65$); [Analysis 12.1](#)
- nausea/vomiting (three trials, N = 2425, RR 0.83, 95% CI 0.68 to 1.01, $P = 0.06$); [Analysis 14.1](#)
- effects on skin (two trials, N = 2227, RR 1.02 95% CI 0.45 to 2.34, $P = 0.96$); [Analysis 18.1](#)
- effects on heart (two trials, N = 1823, RR 1.04 95% CI 0.21 to 5.10, $P = 0.96$); [Analysis 19.1](#)

One trial (GSM-HD 2008) reported severe adverse events grade 3 or 4 split in haematological and non-haematological events during initial chemotherapy. In the BEACOPP arm there were 81% (127/156) participants and in the ABVD arm 43% (72/166) participants affected with haematological events. Non-haematological events could be seen in 19% (30/156) participants from the BEACOPP group and 7% (12/166) of the people belonging to the ABVD group.

There were a number of adverse events which we did not evaluate in this review, however, these are presented in [Table 2](#).

Secondary outcome: quality of life

Quality of life was not reported by any of the included trials. One trial (EORTC 20012) stated in the study protocol that quality of life would be assessed, however, there are no results reported.

Secondary outcome: complete response (CR) rate

Participants

CR rate data were available from five trials (EORTC 20012; GHSG HD14; GHSG HD9; GSM-HD 2008; HD 2000) that included 3427 participants. Data from the parallel randomisation period of the GHSG HD9 trial were not available so we used the provided CR results of all included patients of this trial.

Results

The overall estimate of CR rate showed no evidence for a difference (RR 1.03, 95% CI 1.01 to 1.06, $P = 0.01$, $I^2 = 0\%$) (see [Analysis 21.1](#)).

Secondary outcome: freedom from first progression

Participants

Data of the freedom from first progression was only available from the GSM-HD 2008 trial with 331 participants.

Results

There was a statistically significant evidence for a difference favouring escalated BEACOPP with regard to freedom from first progression (one trial, N = 331, RR 0.46, 95% CI 0.27 to 0.78, $P = 0.004$) see [Analysis 20.1](#).

DISCUSSION

Summary of main results

In this systematic review we analysed the efficacy and safety of escalated BEACOPP and ABVD chemotherapies for the treatment of early unfavourable or advanced stage Hodgkin lymphoma (HL). The results are summarised in the [Summary of findings for the main comparison](#). The findings emerging from these meta-analyses are as follows.

- In contrast to the first version of this review, the present meta-analysis shows evidence for a difference in overall survival (OS), favouring BEACOPP escalated.
- The meta-analysis also showed evidence for an improvement in progression-free survival (PFS) for patients who received BEACOPP escalated.
- There is no evidence for a difference for treatment-related mortality, but it might be higher with BEACOPP escalated.
- The meta-analysis showed a statistically significant higher number of myeloid dysplastic syndrome (MDS) or acute myeloid leukaemia (AML in patients) with advanced HL treated with escalated BEACOPP, but there is no evidence for a difference for overall rate of secondary malignancies between the comparators.
- So far there is not enough evidence to judge the effects of both regimens on infertility. However, available data showed no evidence for a difference between the treatments in patients with advanced HL.
- Treatment with escalated BEACOPP presents evidence for an increase in haematological toxicities WHO grade III or VI, such as anaemia, neutropenia, thrombocytopenia, and infection and non-haematological adverse events like alopecia, mucositis and pain.

- Furthermore, there is no evidence on quality of life due to a lack of data.

Overall completeness and applicability of evidence

All five identified eligible trials have been published, including more than 3000 patients. The trials included adults between 16 and 65 years of age (GHSG HD9: 16 to 65 years; EORTC 20012 and GHSG HD14: 16 to 60 years; GSM-HD 2008: up to 60 years of age; HD 2000: older than 16 years of age) with unfavourable or advanced stage of HL. They provided sufficient evidence with regard to survival outcomes and adverse events but data on long-term toxicity (e.g. infertility, pulmonary and cardiac toxicity) are still insufficient.

Three trials (GSM-HD 2008, HD 2000 and GHSG HD9) had follow-ups of more than five years. However, long-term data from HD 2000 could not be included in the meta-analyses as the time-to-event outcomes have not been reported as hazard ratios (HRs) for each arm and authors did not provide detailed data. Moreover, long-term secondary malignancies could only be evaluated from HD 2000 as the analysis did not adhere to intention-to-treat analysis.

Unfortunately, quality of life was not reported, although evaluated in one trial.

Quality of the evidence

The overall risk of performance and detection bias was low for OS, but was high for other outcomes, as therapy blinding was not feasible. The remaining 'Risk of bias' domains were low and unclear.

The quality of evidence is high for OS, with enough events and precise results allowing meaningful statements. The quality of evidence is moderate for PFS, as the open-label design of the included trials could lead to performance or detection biases. We downgraded by one level for this outcome. The quality of evidence is low for adverse events, due to the small number of events leading to highly imprecise results (downgraded by two points). The quality of evidence for treatment-related mortality and secondary AML or MDS is judged at low, due to a very small number of events leading to very high imprecision (downgraded by two points). The quality of evidence for secondary malignancies is low, downgraded by one point due to small number of events leading to imprecision and downgraded by one point due to indirect results because of the short follow-up period. To detect meaningful differences in terms of secondary malignancies, the follow-up period should be at least 15 years.

The quality of evidence is very low quality for infertility, due to high imprecision, resulting in downgrading by two points. We downgraded one point for indirectness as secondary amenorrhoea

was measured instead of infertility. Moreover, no trial reported results for male fertility.

We did not identify risk of publication bias, as all registered trials are published and we are not aware of further ongoing studies or completed studies that have not been published.

Potential biases in the review process

To prevent bias within the review, only randomised controlled trials (RCTs) were considered. In addition, all important conference proceedings were searched up to their latest issues. We tried to avoid bias by performing all relevant processes in duplicate. We are not aware of any obvious deficiencies in our review process. However, the small number of trials included in this analysis could lead to publication bias, as we could not generate a funnel plot. However, as mentioned before, we did not identify risk of publication bias, as all registered trials are published and we are not aware of further ongoing studies or completed studies that have not been published.

One concern associated with the GHSG HD9 trial was that randomisation to the escalated BEACOPP arm started later than the randomisation to the other two arms. Furthermore, randomisation to the COPP/ABVD arm was stopped after the first interim analysis due to the fact that both BEACOPP groups together were statistically significantly superior to COPP/ABVD in terms of the rate of freedom from treatment failure (Diehl 2003). According to this potential risk of bias, the analyses of OS and PFS were based on data of patients recruited within the same time period (COOPP/ABVD N = 177, BEACOPP N = 265).

In summary, there is maximum likelihood that all relevant studies were identified, all relevant data could be obtained and the review process (searching, data collection, analysis) did not introduce bias into the review.

Agreements and disagreements with other studies or reviews

Within this context two trials (Eich 2010; Ferme 2007a), examined the treatment with four to six cycles ABVD compared to four cycles BEACOPP baseline. Neither showed an advantage of BEACOPP baseline regarding response, freedom from treatment failure/event-free survival, nor OS. However, following the rationale to aim at improved outcomes by dose escalation, the HD14 trial was designed to examine the even more intensive regimen of two cycles of escalated BEACOPP, plus two cycles of ABVD compared to four cycles of ABVD, both followed by 30 Gray involved field radiotherapy (IF-RT) for early unfavourable HL. This further intensification might be a success, because after a median follow-up of 3.5 years the trial showed an improved freedom from treatment failure for patients who received escalated BEACOPP (HR 0.49,

95% CI 0.34 to 0.71), even if a difference with regard to OS was not detectable within this short period (GHSG HD14). The discussion on pros and cons of escalated BEACOPP compared to other treatment options, especially ABVD, for HL patients with advanced-stage disease is active since the GHSG HD9 trial has been published. All included trials in this review that examined patients with newly diagnosed unfavourable or advanced stage HL showed an improved PFS with BEACOPP escalated compared to ABVD. With the inclusion of the recently completed trial EORTC 20012 in the meta-analysis, this increased PFS is now also translated in an overall survival advantage with BEACOPP escalated. This result is in line with a comprehensive network meta-analysis in advanced stage HL patients, favouring BEACOPP escalated over ABVD (Skoetz 2013).

AUTHORS' CONCLUSIONS

Implications for practice

The results of this meta-analysis are based on five trials with more than 3000 patients with Hodgkin lymphoma (HL) aged between 16 and 65 years. It provides high-quality evidence of an improved OS and moderate quality of evidence for an improved PFS for adults with unfavourable or advanced stage HL receiving first-line treatment with escalated BEACOPP compared to ABVD. In people receiving escalated BEACOPP, more acute adverse events occur, but low-quality evidence suggests that this does not lead to a statistical difference in treatment-related mortality. Furthermore, there is only low-quality evidence of a difference in the total number of secondary malignancies, as the follow-up period might be too short to detect meaningful differences. Low-quality evidence also suggests that people treated with escalated BEACOPP may

have a higher risk of developing secondary AML or MDS. Due to the availability of only very low-quality evidence available, we are unable to come to a conclusion in terms of infertility. This review does for the first time suggest a survival benefit. However, it is clear from this review that BEACOPPesc may be more toxic than ABVD, and very important long-term side effects of second malignancies and infertility have not been sufficiently analysed yet.

Implications for research

Information regarding quality of life as well as long-term toxicity (e.g. infertility, secondary malignancies, cardiac toxicity), should be of major concern for further research since most patients are diagnosed in the second or third decade of life and HL has become a curable disease for the majority of affected patients.

Modifications of the BEACOPP escalated regimen including newer drugs and possibly less side effects are being tested by the German Hodgkin Lymphoma Study Group to overcome adverse events, results are expected soon.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

EORTC 20012

Methods	<p>Randomisation</p> <ul style="list-style-type: none"> • A randomised controlled trial with two arms: 4 escalated plus 4 standard courses of BEACOPP versus 8 courses of ABVD <p>Recruitment period</p> <ul style="list-style-type: none"> • 2002 to 2010 <p>Median follow-up time</p> <ul style="list-style-type: none"> • 3.8 years
Participants	<p>Eligibility criteria:</p> <ul style="list-style-type: none"> • patients with untreated histologically documented HL • no prior therapy for HL • clinical stage: III or IV disease • at least 1 two-dimensionally measurable target lesion or extranodal lesion • international prognostic score of at least 3 • performance status: WHO 0 to 3 • hematopoietic: WBC greater than 2000/mm³, platelet count greater than 100,000/mm³ • hepatic: no prior uncontrolled hepatitis B viral infection, bilirubin no greater than 2.5 times normal (unless due to HL) • renal: creatinine no greater than 2.0 mg/dL (unless due to HL) • cardiovascular: no severe cardiac disease that would limit normal life expectancy or preclude study, LVEF at least 50% • pulmonary: no severe pulmonary disease that would limit normal life expectancy or preclude study, respiratory function at least 30% • HIV negative • HTLV1 negative • no severe active infection • no severe neurological or metabolic disease that would limit normal life expectancy or preclude study • no other prior or concurrent malignancy except basal cell skin cancer or carcinoma in situ of the cervix • no psychological, familial, sociological, or geographical condition that would preclude study • not pregnant or nursing • fertile patients must use effective contraception • no concurrent radiotherapy • patients between 16 years and 60 years <p>Patients recruited (not known)</p> <ul style="list-style-type: none"> • escalated BEACOPP (N = 274): 10 patients crossed over to ABVD • ABVD (N = 275): 5 patients crossed over to BEACOPP <p>Mean age:</p> <ul style="list-style-type: none"> • 35.2 years <p>Gender (male, female):</p> <ul style="list-style-type: none"> • males 75%, females 25%

	Country <ul style="list-style-type: none"> European Organization for Research and Treatment of Cancer
Interventions	escalated BEACOPP (every 22 days), (no information about dosage) <ul style="list-style-type: none"> Patients receive doxorubicin IV over 5 minutes and cyclophosphamide IV on day 1; etoposide IV over 30 minutes on days 1 to 3; oral procarbazine on days 1 to 7; oral prednisone on days 1 to 14; and vincristine IV and bleomycin IV or intramuscularly (IM) on day 8. Patients may receive dexamethasone in place of prednisone. Patients also receive filgrastim (G-CSF) subcutaneously (SC) beginning on day 9 and continuing until blood counts recover or pegfilgrastim SC on day 9 only. ABVD (every 28 days) (no information about doses) <ul style="list-style-type: none"> Patients receive doxorubicin IV over 5 minutes, bleomycin IV or IM, vinblastine IV, and dacarbazine IV over 5 to 10 minutes on days 1 and 15. Additional therapy <ul style="list-style-type: none"> no irradiation
Outcomes	Outcomes and time points from the registered protocol of the study that are considered in the review: reported <ul style="list-style-type: none"> EFS OS PFS CR rate Time to progression Quality of life Adverse events (secondary malignancies) not reported <ul style="list-style-type: none"> Adverse events (treatment-related mortality, Haematological grade III or IV toxicity, infertility, cardiopulmonary toxicity) Quality of life
Notes	None

Risk of bias**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Between October 2002 and January 2010, 550 patients were randomly assigned."
Allocation concealment (selection bias)	Low risk	Quote: "Random assignments were stratified by institution and JPS ..."
Blinding (performance bias and detection bias) Overall survival	Low risk	No information about blinding provided. This is judged not to be a source of bias for OS

Blinding (performance bias and detection bias) Other outcomes	High risk	No information about blinding provided, blinding in this setting uncommon
Incomplete outcome data (attrition bias) Overall Survival	Low risk	CONSORT flow diagram provided.
Selective reporting (reporting bias)	High risk	Comment: The protocol was registered at http://clinicaltrials.gov (Identifier: NCT00049595). The authors recognised all predefined outcomes except quality of life
Other bias	Unclear risk	No information provided.

GHSG HD14

Methods	<p>Randomisation</p> <ul style="list-style-type: none"> • A randomised controlled trial with two arms: 2 courses of escalated BEACOPP followed by 2 courses of ABVD plus involved field radiotherapy (IF-RT) arm versus 4 courses of ABVD plus IF-RT arm. <p>Allocation ratios</p> <ul style="list-style-type: none"> • 1:1 <p>Recruitment period</p> <ul style="list-style-type: none"> • from January 2003 to July 2008 <p>Median follow-up time</p> <ul style="list-style-type: none"> • 43 months
Participants	<p>Eligibility criteria:</p> <ul style="list-style-type: none"> • patients with previously untreated HL • clinical stage: IA, IB, IIA (with one of the following risk factors: large mediastinal mass (a), extranodal disease (b), elevated erythrocyte sedimentation rate (c), or ≥ 3 nodal areas (d)), IIB (with risk factors c and d) • age: 16 to 60 years <p>Patients recruited (N = 1655),</p> <ul style="list-style-type: none"> • BEACOPP analysed (N = 763), excluded: 15 not sufficiently documented, 42 violation of inclusion criteria • ABVD analysed (N = 765) excluded: 17 not sufficiently documented, 53 violation of inclusion criteria <p>Mean age:</p> <ul style="list-style-type: none"> • for both arms 32 years (range, 18 to 60 years) <p>Gender (male, female):</p> <ul style="list-style-type: none"> • male 47.7%, female 53.3% <p>Stage of disease:</p> <ul style="list-style-type: none"> • for both arms: stage I 4.8%, stage II 95.2% <p>Country</p> <ul style="list-style-type: none"> • Germany, Switzerland, Netherlands, Czech Republic, Austria

Interventions	<p>BEACOPP (repeated on day 22)</p> <ul style="list-style-type: none"> cyclophosphamide 1,250 mg/m² (day 1), doxorubicin 35 mg/m² (day 1), etoposide 200 mg/m² (days 1 to 3), procarbazine 100 mg/m² (days 1 to 7), prednisone 40 mg/m² (days 1 to 14), vincristine 1.4 mg/m² (day 8; maximum, 2 mg), and bleomycin 10 mg/m² (day 8). G-CSF had to be administered from day 8 of each BEACOPPesc cycle until recovery of WBC to at least 1,000/L on 3 consecutive days. <p>ABVD (repeated on day 29)</p> <ul style="list-style-type: none"> doxorubicin 25 mg/m² (days 1 and 15), bleomycin 10 mg/m² (days 1 and 15), vinblastine 6 mg/m² (days 1 and 15), and dacarbazine 375 mg/m² (days 1 and 15). G-CSF was administered if clinically indicated, starting from day 7 or 21 <p>After chemotherapy all patients received IF-RT</p> <ul style="list-style-type: none"> 30 Gray <p>Others: Treatment was postponed until recovery of WBC to at least 2 500/L and platelet count to at least 80 000/L on the day scheduled for re-treatment. In cases of treatment postponement of more than 2 weeks or pronounced toxicity during treatment, dose reductions were foreseen in the trial protocol</p>
Outcomes	<p>Outcomes and time points from the study that are considered in the review:</p> <p>reported</p> <ul style="list-style-type: none"> OS (4-year outcome) CR rate PFS (4-year outcome) Adverse events (haematological grade III or IV toxicity, secondary malignancies, treatment-related mortality, infertility) <p>not reported</p> <ul style="list-style-type: none"> Adverse events (cardiopulmonary toxicity) Time to progression
Notes	<p>Supported by Grant No. 106164 from German Cancer Aid (Deutsche Krebshilfe) and the Swiss Federal Government</p> <p>Employment or Leadership Position: None Consultant or Advisory</p> <p>Role: None, Stock Ownership: None, Honoraria: None, Research Funding: None, Expert Testimony: None, Other, Remuneration: JuliaMeissner, Amgen, Celgene</p>

Risk of bias

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote: "patients (...) were randomized"</p> <p>Comment: The HD 14 trial is organized by the GHSg, that also led the HD 9 trial. Sequence generation and allocation concealment should be judged to probably be adequate, because this is a large multi-centre trial and other trials of this study group have previously been adequately randomised and allocation of these trials have previously been adequately concealed</p>

GHSG HD14 (Continued)

Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias) Overall survival	Low risk	No information about blinding provided. This is judged not to be a source of bias for OS
Blinding (performance bias and detection bias) Other outcomes	High risk	No information about blinding provided, blinding in this setting uncommon
Incomplete outcome data (attrition bias) Overall Survival	Low risk	Quote: “[...] 1.655 patients [...] were randomized. [...] The full analysis set comprised 1623 patients [...]. Patient characteristics were well balanced between both arms [...].” Comment: Missing outcome data are balanced in numbers across intervention groups, with similar reasons for missing data across groups
Selective reporting (reporting bias)	Unclear risk	A protocol of this trial was not registered.
Other bias	Unclear risk	When the third planned interim analysis yielded a significant group sequential test (adjusted overall P.0452), the trial was stopped according to protocol

GHSG HD9

Methods	<p>Randomisation</p> <ul style="list-style-type: none"> • A randomised controlled trial with three arms: <ol style="list-style-type: none"> 1. 8 escalated courses of BEACOPP 2. 8 standard courses of BEACOPP 3. 8 courses of cyclophosphamide, vincristine, procarbazine, and prednisone (COPP) alternating with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). <p>Allocation ratios</p> <ul style="list-style-type: none"> • Randomisation to the COPP/ABVD-arm was stopped after first interim analysis due to the fact that both BEACOPP groups together were significantly superior to COPP/ABVD in terms of the rate of freedom from treatment failure (Diehl 2003). Subsequently, unequal randomization probabilities were used to equalize the numbers in each group. <p>Recruitment period</p> <ul style="list-style-type: none"> • from February 1993 to March 1998. <p>Median follow-up time</p> <ul style="list-style-type: none"> • 111 months (range 3 to 167 months).
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Participants	<p>Eligibility criteria:</p> <ul style="list-style-type: none"> patients with histologically documented, previously untreated HL clinical stage: IIB or IIIA (with a large mediastinal mass, i.e. > one third of the maximal thoracic diameter, or extranodal lesions or massive spleen involvement, i.e. with diffuse infiltration or five local lesions), IIIA (with at least three involved nodal areas or elevated erythrocyte sedimentation rate, i.e. more than 50 mm/h in asymptomatic patients and more than 30 mm/h in patients with B symptoms), IIIB, IV Karnofsky performance status higher than 70% age between 16 and 65 years not positive for HIV free of concurrent disease patients must have provided written informed consent <p>Patients recruited (N = 1282)</p> <ul style="list-style-type: none"> escalated BEACOPP (N = 496): excluded (N = 28, 27 because of revised histology or met clinical exclusion criteria, 1 declined to give consent), eligible (N = 468), analysed (N = 466, two eligible were excluded because they were lost to follow-up) standard BEACOPP (N = 498): excluded (N = 28, all because of revised histology or met clinical exclusion criteria), eligible (N = 470), analysed (N = 469, one eligible was excluded because they were lost to follow-up) COPP/ABVD (N = 288): excluded (N = 25, all because of revised histology or met clinical exclusion criteria), eligible (N = 263), analysed (N = 261, three eligible were excluded because they were lost to follow-up). Randomisation to the COPP/ABVD-arm was stopped after first interim analysis due to the fact that both BEACOPP groups together were significantly superior to COPP/ABVD in terms of the rate of freedom from treatment failure (Diehl 2003). <p>Mean age:</p> <ul style="list-style-type: none"> escalated: BEACOPP 32 years (15% of 466 patients were 50 to 65 years old); standard: BEACOPP 33 years (18% of 469 patients were 50 to 65 years old); COPP/ABVD: 32 years (16% of 260 patients were 50 to 65 years old) <p>Gender (male, female):</p> <ul style="list-style-type: none"> escalated BEACOPP: 289, 177; standard BEACOPP: 295, 174; COPP/ABVD: 149, 112 <p>Stage of disease:</p> <ul style="list-style-type: none"> Stage IIB: escalated BEACOPP: 16%; standard BEACOPP: 14%; COPP/ABVD: 9% Stage III: escalated BEACOPP: 52%; standard BEACOPP: 52%; COPP/ABVD: 60% Stage IV: escalated BEACOPP: 33%; standard BEACOPP: 35%; COPP/ABVD: 32% <p>Bulky disease: escalated BEACOPP: 67%; standard BEACOPP: 68%; COPP/ABVD: 58%</p> <p>Country</p> <ul style="list-style-type: none"> Germany, Switzerland, Austria, Czech Republic
Interventions	<p>escalated BEACOPP (every 22 days)</p> <ul style="list-style-type: none"> bleomycin (10 mg/m², day 8), etoposide (200 mg/m², day 1 - 3), doxorubicin (35 mg/m², day 1), cyclophosphamide (1200 mg/m², day 1), vincristine (1.4 mg/m² (2 mg/m² maximum), day 8), procarbazine (100 mg/m², day 1 - 7), prednisone (40 mg/m², day 1 - 14)

	<p>standard BEACOPP (every 22 days)</p> <ul style="list-style-type: none"> bleomycin (10 mg/m², day 8), etoposide (100 mg/m², day 1 - 3), doxorubicin ([25 mg/m², day 1), cyclophosphamide (650 mg/m², day 1)], vincristine (1.4 mg/m² (2 mg/m² maximum), day 8], procarbazine (100 mg/m², day 1 - 7), prednisone (40 mg/m², day 1 - 14) <p>COPP/ABVD (every 57 days)</p> <ul style="list-style-type: none"> bleomycin (10 mg/m², day 29 and 43), doxorubicin (25 mg/m², day 29 and 43), cyclophosphamide (650 mg/m², day 1 and 8), vincristine (1.4 mg/m² (2 mg/m² maximum), day 1 and 8), procarbazine (100 mg/m², day 1 - 14), prednisone (40 mg/m², day 1 - 14), vinblastine (6 mg/m², day 29 and 43), dacarbazine (375 mg/m², day 29 and 43) <p>Additional therapy</p> <p>At the end of chemotherapy, radiotherapy was scheduled for sites of initial bulky disease (those at least 5 cm in diameter) and any residual tumour</p> <ul style="list-style-type: none"> 30 Gray for initial bulky disease 40 Gray for any residual tumour
Outcomes	<p>Outcomes and time points from the study that are considered in the review: reported</p> <ul style="list-style-type: none"> OS (10-year outcome) FFTF (analysed as PFS in this review) CR Adverse events (treatment-related mortality, Haematological grade III or IV toxicity, secondary malignancies, infertility) <p>not reported</p> <ul style="list-style-type: none"> Time to progression Adverse events (cardiopulmonary toxicity)
Notes	<p>At the first interim analysis in September 1996, the early stopping boundary was crossed, with the demonstration that both BEACOPP groups together were significantly superior to COPP/ABVD in terms of the rate of FFTF. Therefore, assignment to the COPP/ABVD group was stopped (Diehl 2003a).</p> <p>This study was supported by a grant from: Deutsche Krebshilfe, Swiss Group for Clinical Cancer Research (Diehl 2003a)</p> <p>The author(s) indicated no potential conflicts of interest (Engert 2009).</p>

<i>Risk of bias</i>			<i>Risk of bias</i>
Bias	Authors' judgement	Support for judgement	
Random sequence generation (selection bias)	Low risk	Quote: "random assignment was performed by computer"	
Allocation concealment (selection bias)	Low risk	Quote: "after clinical staging patients were randomly assigned by telephone call to the trial coordination center to one of three chemotherapy regimens"	

GHSG HD9 (Continued)

Blinding (performance bias and detection bias) Overall survival	Low risk	No information about blinding provided. This is judged not to be a source of bias for OS
Blinding (performance bias and detection bias) Other outcomes	High risk	No information about blinding provided, blinding in this setting uncommon
Incomplete outcome data (attrition bias) Overall Survival	Low risk	Quote: "Of 1282 patients, 86 were excluded due to incorrect diagnosis, concurrent disease, incorrect staging, other clinical exclusion criteria and insufficient data to determine the treatment outcome. Thus, a total of 1196 patients were fully assessable" Comment: Missing outcome data are balanced in numbers across intervention groups, with similar reasons for missing data across groups. Therefore, see Diehl 2003a who has given a detailed overview of the reasons for the exclusion of patients: escalated BEACOPP (15 did not have HD, 12 met clinical exclusion criteria, 1 lost to follow-up), standard BEACOPP (19 did not have HD, 9 met clinical exclusion criteria, 1 lost to follow-up), COPP/ABVD (12 did not have HD, 13 met clinical exclusion criteria, 3 lost to follow-up)
Selective reporting (reporting bias)	Unclear risk	A protocol of this trial was not registered.
Other bias	Unclear risk	Quote: "Assignment to the COPP/ABVD group was stopped by the safety board after the first interim analysis indicating that both BEACOPP groups were significantly superior in terms of FFTF to COPP/ABVD (P .03)." Comment: In the GHSG HD9 trial randomisation for the escalated BEACOPP-arm started later than randomisation to both other arms. Furthermore, randomisation to the COPP/ABVD-arm was stopped after first interim analysis due to the fact that both BEACOPP groups together were significantly superior to COPP/ABVD in terms of the rate of freedom from treatment failure (Diehl 2003). According to this potential risk of bias the analyses of

		OS and PFS were based on data of patients recruited in parallel, i.e. during the same time period (COPP/ABVD N = 177, BEA-COPP N = 265)
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GSM-HD 2008

Methods	<p>Randomisation</p> <ul style="list-style-type: none"> • A randomised controlled trial with two arms: 4 escalated plus 4 standard courses of BEACOPP versus 6-8 courses of ABVD <p>Allocation ratios</p> <ul style="list-style-type: none"> • 1:1 <p>Recruitment period</p> <ul style="list-style-type: none"> • from March 2000 to March 2007. <p>Median follow-up time</p> <ul style="list-style-type: none"> • 61 months (range not reported).
Participants	<p>Eligibility criteria</p> <ul style="list-style-type: none"> • patients with histologically documented HL • clinical stage: IIB, III, IV or ≥ 3 international-prognostic-score HL • no previous anticancer treatment • adequate bone marrow, renal and hepatic function • absence of severe cardiac disease and LVEF $\geq 50\%$ • absence of lung diseases • absence of previous invasive cancer • absence of HIV • adult patients up to 60 years of age <p>Patients recruited (331 patients)</p> <ul style="list-style-type: none"> • BEACOPP (N = 163 were analysed) • ABVD (N = 168 were analysed) <p>Mean age:</p> <ul style="list-style-type: none"> • not reported. (escalated BEACOPP 20% of 155 patients ≥ 45 years; ABVD 23% of 166 patients ≥ 45 years) <p>Gender (male, female):</p> <ul style="list-style-type: none"> • escalated BEACOPP: 88, 66; ABVD: 100, 66 <p>Stage of disease:</p> <ul style="list-style-type: none"> • not reported. <p>Country</p> <ul style="list-style-type: none"> • Italy
Interventions	<p>escalated BEACOPP (every 21 days)</p> <ul style="list-style-type: none"> • bleomycin [10 mg/m², day 8], etoposide [200 mg/m², day 1-3], doxorubicin [35 mg/m², day 1], cyclophosphamide [1250 mg/m², day 1], vincristine [1.4 mg/m² (2 mg/m² maximum), day 8], procarbazine [100 mg/m², day 1-7], prednisone [40 mg/m², day 1-14], G-CSF [no information about dosage and period of application] <p>standard BEACOPP (every 21 days)</p> <ul style="list-style-type: none"> • bleomycin [10 mg/m², day 8], etoposide [100 mg/m², day 1-3], doxorubicin [25 mg/m², day 1], cyclophosphamide [650 mg/m², day 1], vincristine [1.4 mg/m² (2 mg/m² maximum), day 8], procarbazine [100 mg/m², day 1-7], prednisone [40 mg/m²,

	<p>day 1-14]</p> <p>ABVD (every 28 days)</p> <ul style="list-style-type: none"> doxorubicin [25 mg/m², day 1 and 15], bleomycin [10 mg/m², day 1 and 15], vinblastine [6 mg/m², day 1 and 15], dacarbazine [375 mg/m², day 1 and 15] <p>Additional therapy</p> <p>At the end of chemotherapy, radiotherapy was scheduled for sites of initial bulky disease and any residual tumour</p> <ul style="list-style-type: none"> 30 Gray <p>For treatment failures</p> <ul style="list-style-type: none"> re-induction chemotherapy followed by stem-cell supported BEAM plus up to 25 Gray radiotherapy
Outcomes	<p>Outcomes and time points from the study that are considered in the review:</p> <p>reported</p> <ul style="list-style-type: none"> OS (3-year outcome) EFS (analysed as PFS in this review) CR rate Adverse events (Haematological grade III or IV toxicity, secondary malignancies, cardiopulmonary toxicity) <p>not reported</p> <ul style="list-style-type: none"> Time to progression Adverse events (infertility)
Notes	<p>Funding resources: The study was designed by the investigators, and the coordination of the study, the collection and quality control of the data, and the statistical analyses were performed at the operations office of Fondazione Michelangelo (the sponsoring organization). No commercial support was provided</p> <p>The author(s) indicated no potential conflicts of interest.</p>

<i>Risk of bias</i>			<i>Risk of bias</i>
Bias	Authors' judgement	Support for judgement	
Random sequence generation (selection bias)	Unclear risk	Quote: "patients (...) were randomized" Comment: No further information provided	
Allocation concealment (selection bias)	Unclear risk	No information provided.	
Blinding (performance bias and detection bias) Overall survival	Low risk	No information about blinding provided. This is judged not to be a source of bias for OS	
Blinding (performance bias and detection bias) Other outcomes	High risk	No information about blinding provided, blinding in this setting uncommon	

Incomplete outcome data (attrition bias) Overall Survival	Low risk	Quote: “a total of 331 patients were recruited (...); 168 patients were assigned to receive ABVD and 163 to receive BEACOPP. Two patients were subsequently found to be ineligible because of a wrong diagnosis, and 7 withdrew consent before starting chemotherapy. Thus, 166 patients were initiated on ABVD chemotherapy and 156 on BEACOPP chemotherapy (safety population), whereas all 331 patients who underwent randomization were assessed for efficacy (intention-to-treat population).”
Selective reporting (reporting bias)	Low risk	All outcomes reported as pre-planned
Other bias	Unclear risk	No information provided.

HD 2000

Methods	<p>Randomisation</p> <ul style="list-style-type: none"> • A randomised controlled trial with three arms: 4 escalated plus 2 standard courses of BEACOPP versus 6 courses of CEC (cyclophosphamide, lomustine, vindesine, melphalan, prednisone, epidoxorubicin, vincristine, procarbazine, vinblastine, and bleomycin) versus 6 courses of ABVD arm. <p>Allocation ratios</p> <ul style="list-style-type: none"> • 1:1:1 <p>Recruitment period</p> <ul style="list-style-type: none"> • from April 2000 to June 2007. <p>Median follow-up time</p> <ul style="list-style-type: none"> • 41 months (range 4 to 91 months).
Participants	<p>Eligibility criteria.</p> <ul style="list-style-type: none"> • patients with histologically documented, previously untreated HL, • clinical stage: IIB, III, IV • Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 3 • age >16 years • patients must have provided written informed consent <p>Patients recruited (N = 307)</p> <ul style="list-style-type: none"> • BEACOPP (N = 102): excluded (N = 2, one because of revised histology, one because of not compliant), eligible (N = 100), analysed (N = 98, two eligible were excluded because of missing data) • CEC (N = 102): excluded (N = 0), eligible (N = 102), analysed (N = 98, three eligible were excluded because of missing data, one because of lost of follow-up) • ABVD (N = 103): excluded (N = 0), eligible (N = 103), analysed (N = 99, three eligible were excluded because of missing data, one because of lost of follow-up) <p>Mean age:</p> <ul style="list-style-type: none"> • escalated BEACOPP: 29 years (17% of 98 patients $\geq$ 45 years); CEC: 33 years (26% of 98 patients $\geq$ 45 years); ABVD: 32 years (18% of 99 patients $\geq$ 45 years)

	<p>Gender (male, female):</p> <ul style="list-style-type: none"> escalated BEACOPP: 60, 38; CEC: 56, 42; ABVD: 43, 56 <p>Stage of disease:</p> <ul style="list-style-type: none"> Stage IIB: escalated BEACOPP: 31%; CEC: 29%; ABVD: 33% Stage III: escalated BEACOPP: 46%; CEC: 45%; ABVD: 44% Stage IV: escalated BEACOPP: 22%; CEC: 26%; ABVD: 22% <p>Bulky disease: escalated BEACOPP: 37%; CEC: 37%; ABVD: 31%</p> <p>Country</p> <ul style="list-style-type: none"> Italy
Interventions	<p>BEACOPP (every 21 days)</p> <ul style="list-style-type: none"> bleomycin [10 mg/m² intravenously, day 8], etoposide [200 (escalated) -100 (standard) mg/m² intravenously, day 1-3], doxorubicin [35 (escalated)-25 (standard) mg/m² intravenously, day 1], cyclophosphamide [1250 (escalated)-650 (standard) mg/m² intravenously, day 1], vincristine [1.4 mg/m² (2 mg/m² maximum) intravenously, day 8], procarbazine [100 mg/m² orally, day 1-7], prednisone [40 mg/m² orally, day 1-14], G-CSF [300 µg total subcutaneously, day 8 until neutrophils 0.5/µL] <p>CEC (every 28 days)</p> <ul style="list-style-type: none"> cyclophosphamide [650 mg/m² intravenously, day 1 (cycles 1, 3 and 5 only)], lomustine [100 mg/m² orally, day 1 (cycles 2, 4 and 6 only)], vindesine [3 mg/m² intravenously, day 1], melphalan [6 mg/m² orally, day 1-3], prednisone [40 mg/m² orally, day 1-14], epidoxorubicin [40 mg/m² intravenously, day 8], vincristine [1.4 mg/m² (2 mg/m² maximum) intravenously, day 8], procarbazine [100 mg/m² orally, day 8-14], vinblastine [6 mg/m² intravenously, day 15], bleomycin [10 mg/m² intravenously, day 15] <p>ABVD (every 28 days)</p> <ul style="list-style-type: none"> doxorubicin [25 mg/m² intravenously, day 1 and 15], bleomycin [10 mg/m² intravenously, day 1 and 15], vinblastine [6 mg/m² intravenously, day 1 and 15], dacarbazine [375 mg/m² intravenously, day 1 and 15] <p>Additional therapy</p> <p>At the end of chemotherapy, radiotherapy was scheduled for sites of previous bulky disease or on slowly or partially responding sites</p> <ul style="list-style-type: none"> 30 to 36 Gray with a boost of 6 additional Gray to persisting disease sites
Outcomes	<p>Outcomes and time points from the study that are considered in the review: reported</p> <ul style="list-style-type: none"> OS (5-year outcome) PFS (5-year outcome) CR rate Adverse events (Haematological grade III or IV toxicity) <p>not reported</p> <ul style="list-style-type: none"> Time to progression Adverse events (treatment-related mortality, cardiopulmonary toxicity, secondary malignancies, infertility)
Notes	<p>This study was in parts funded by: Associazione Angela Serra per la Ricerca sul Cancro, Modena, and the Gruppo Amici Dell'Ematologia, Reggio Emilia, Italy</p> <p>The author(s) indicated no potential conflicts of interest.</p>

<i>Risk of bias</i>		<i>Risk of bias</i>
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomly assigned" Comment: No further information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) Overall survival	Low risk	No information about blinding provided. This is judged not to be a source of bias for OS
Blinding (performance bias and detection bias) Other outcomes	High risk	No information about blinding provided, blinding in this setting uncommon
Incomplete outcome data (attrition bias) Overall Survival	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups (i.e. 4 patients of the BEACOPP arm were excluded from the analyses because of revised histology (N = 1), not compliant (N = 1), missing data (N = 2); 4 patients of the ABVD arm were excluded because of missing data (N = 3) and lost to follow-up (N = 1))
Selective reporting (reporting bias)	Unclear risk	Although the protocol is published, no pre-planned outcomes are reported, therefore we judge the risk of bias as unclear
Other bias	Unclear risk	Quote: "The study was initially designed to compare myelotoxicity referred of leukopenia of CEC and BEACOPP regimens with respect of that of ABVD (...). Once, in the first 18 months, Gruppo Italiano per lo Studio dei Linfomi centers became familiar with BEACOPP, the protocol was amended and BEACOPP and CEC regimens were tested against ABVD primarily in terms of FFS." Quote: "We used one-sided test in consideration of the expected superiority of BEACOPP and CEC, in term of FFS in comparison with the historical knowledge about ABVD chemotherapy regimen."

	Comment: This procedure might have led to a underpowered study
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Abbreviations: **CR** - complete response; **EFS** - event-free survival; **FFTF** - freedom from treatment failure; **G-CSF** - Granulocyte-colony stimulating factor; **HD** - Hodgkin's disease; **HL** - Hodgkin lymphoma; **HTLV** - human T-cell lymphotropic virus; **LVEF** - left ventricular ejection fraction; **OS** - overall survival; **PFS** - progression-free survival; **WBC** - white blood cell

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Ballova 2005	Comparison arm not treated with escalated BEACOPP chemotherapy
Biasoli 2008	Not a randomised controlled trial
Borchmann 2011	Control arm not treated with ABVD chemotherapy
Borchmann 2017	Comparison arm not treated with ABVD chemotherapy
Canellos 2005	Review
Cheson 2007	Review
Connors 2002	Review
Dann 2012	Not a randomised controlled trial
DeVita 2003	Review
Diehl 1997	Not a randomised controlled trial
Economopoulos 2003	Not a randomised controlled trial
Eghbali 2005	Review
Eich 2004	Comparison arm not treated with escalated BEACOPP chemotherapy
Elbl 2004	Not a randomised controlled trial
Elbl 2006	Not a randomised controlled trial
Engert 2007	Comparison arm not treated with escalated BEACOPP chemotherapy
Engert 2012	Control arm not treated with ABVD chemotherapy

(Continued)

Ferme 2002	Comparison arms not treated with escalated BEACOPP chemotherapy
Ferme 2007	Comparison arms not treated with escalated BEACOPP chemotherapy
Franklin 1999	Comparison arm not treated with escalated BEACOPP chemotherapy
Franklin 2002	Review
Goldstone 1998	Review
Hampton 2008	Review
Italiano 2006	Review
Johnson 2016	All PET-positive patients received BEACOPP chemotherapy
Kelly 2002	Not a randomised controlled trial
Koumarianou 2007	Not a randomised controlled trial
Niitsu 2006	Not a randomised controlled trial
Portlock 1999	Review
Proctor 2005	Review
Sieber 1999	Comparison arm not treated with escalated BEACOPP chemotherapy
Sieniawski 2008	Comparison arm not treated with escalated BEACOPP chemotherapy
Sieniawski 2008a	Control arm not treated with ABVD chemotherapy
Tesch 1995	Not a randomised controlled trial
Tesch 1996	Not a randomised controlled trial
Tesch 1998	Not a randomised controlled trial
Van der Kaaij 2007	Comparison arm not treated with escalated BEACOPP chemotherapy

ABVD - doxorubicin/bleomycin/vinblastine/dacarbazine; **BEACOPP** - bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; PET - Positron emission tomography

DATA AND ANALYSES

Comparison 1. Analysis overall survival

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 OS - all - same recruitment period between the 2 arms (HD9)	5	3142	Hazard Ratio (Fixed, 95% CI)	0.74 [0.57, 0.97]
2 OS subgrouped by stage of disease	5	3142	Hazard Ratio (Fixed, 95% CI)	0.75 [0.57, 0.97]
2.1 early unfavourable stage	1	1623	Hazard Ratio (Fixed, 95% CI)	1.02 [0.54, 1.91]
2.2 advanced stage	4	1519	Hazard Ratio (Fixed, 95% CI)	0.70 [0.52, 0.93]
3 OS subgrouped by treatment	5	3142	Hazard Ratio (Fixed, 95% CI)	0.75 [0.57, 0.97]
3.1 only ABVD regimen	4	2700	Hazard Ratio (Fixed, 95% CI)	0.83 [0.60, 1.14]
3.2 ABVD including regimen	1	442	Hazard Ratio (Fixed, 95% CI)	0.62 [0.40, 0.96]
4 OS subgrouped by number of cycles of escalated BEACOPP	5	3142	Hazard Ratio (Fixed, 95% CI)	0.75 [0.57, 0.97]
4.1 eight cycles of escalated BEACOPP	1	442	Hazard Ratio (Fixed, 95% CI)	0.62 [0.40, 0.96]
4.2 four cycles of escalated BEACOPP	3	1077	Hazard Ratio (Fixed, 95% CI)	0.76 [0.52, 1.12]
4.3 two cycles of escalated BEACOPP	1	1623	Hazard Ratio (Fixed, 95% CI)	1.02 [0.54, 1.91]
5 OS subgrouped by length of follow-up	5	3142	Hazard Ratio (Fixed, 95% CI)	0.75 [0.57, 0.97]
5.1 short-term follow-up (median length up to 5 years)	4	2700	Hazard Ratio (Fixed, 95% CI)	0.83 [0.60, 1.14]
5.2 long-term follow-up (median length 10 years)	1	442	Hazard Ratio (Fixed, 95% CI)	0.62 [0.40, 0.96]
6 OS subgrouped by radiotherapy	5	3132	Hazard Ratio (Fixed, 95% CI)	0.75 [0.57, 0.97]
6.1 without radiotherapy	1	549	Hazard Ratio (Fixed, 95% CI)	0.71 [0.42, 1.20]
6.2 with radiotherapy	4	2583	Hazard Ratio (Fixed, 95% CI)	0.76 [0.56, 1.02]
7 OS - all recruited patients (HD9) with potential risk of bias due to different time periods of recruitment	5		Hazard Ratio (Fixed, 95% CI)	0.66 [0.52, 0.84]

Comparison 2. Analysis of progression-free survival (PFS)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 PFS - all - same recruitment period between the 2 arms (HD9)	5	3142	Hazard Ratio (Fixed, 95% CI)	0.54 [0.45, 0.64]
2 PFS subgrouped by stage of disease	5	3142	Hazard Ratio (Fixed, 95% CI)	0.54 [0.45, 0.64]
2.1 early unfavourable stage	1	1623	Hazard Ratio (Fixed, 95% CI)	0.47 [0.31, 0.71]
2.2 advanced stage	4	1519	Hazard Ratio (Fixed, 95% CI)	0.56 [0.46, 0.67]
3 PFS subgrouped by treatment	5	3142	Hazard Ratio (Fixed, 95% CI)	0.54 [0.45, 0.64]
3.1 only ABVD regimen	4	2700	Hazard Ratio (Fixed, 95% CI)	0.55 [0.45, 0.67]
3.2 ABVD including regimen	1	442	Hazard Ratio (Fixed, 95% CI)	0.50 [0.34, 0.72]
4 PFS subgrouped by number of cycles of escalated BEACOPP	5	3142	Hazard Ratio (Fixed, 95% CI)	0.54 [0.45, 0.64]
4.1 eight cycles of escalated BEACOPP	1	442	Hazard Ratio (Fixed, 95% CI)	0.50 [0.34, 0.72]
4.2 four cycles of escalated BEACOPP	3	1077	Hazard Ratio (Fixed, 95% CI)	0.58 [0.46, 0.72]
4.3 two cycles of escalated BEACOPP	1	1623	Hazard Ratio (Fixed, 95% CI)	0.47 [0.31, 0.71]
5 PFS subgrouped by length of follow-up	5	3142	Hazard Ratio (Fixed, 95% CI)	0.54 [0.45, 0.64]
5.1 short-term follow-up (median length up to 5 years)	4	2700	Hazard Ratio (Fixed, 95% CI)	0.55 [0.45, 0.67]
5.2 long-term follow-up (median length 10 years)	1	442	Hazard Ratio (Fixed, 95% CI)	0.50 [0.34, 0.72]
6 PFS subgrouped by type of radiotherapy	5		Hazard Ratio (Fixed, 95% CI)	0.54 [0.45, 0.64]
6.1 without radiotherapy	1		Hazard Ratio (Fixed, 95% CI)	0.58 [0.39, 0.86]
6.2 with radiotherapy	4		Hazard Ratio (Fixed, 95% CI)	0.53 [0.44, 0.64]
7 PFS - all recruited patients (HD9) with potential risk of bias due to different time periods of recruitment	5		Hazard Ratio (Fixed, 95% CI)	0.51 [0.43, 0.60]

Comparison 3. Analysis of treatment-related mortality

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment-related mortality	4	2700	Risk Ratio (M-H, Fixed, 95% CI)	2.15 [0.93, 4.95]
2 TRM subgrouped by stage of disease	4	2700	Risk Ratio (M-H, Fixed, 95% CI)	2.15 [0.93, 4.95]
2.1 early unfavourable stage	1	1623	Risk Ratio (M-H, Fixed, 95% CI)	9.15 [0.49, 169.58]
2.2 advanced stage	3	1077	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [0.69, 4.13]

Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma (Review)

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3 TRM subgrouped by number of cycles of escalated BEACOPP	4	2700	Risk Ratio (M-H, Fixed, 95% CI)	2.15 [0.93, 4.95]
3.1 four cycles of escalated BEAOPP	3	1077	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [0.69, 4.13]
3.2 two cycles of escalated BEACOPP	1	1623	Risk Ratio (M-H, Fixed, 95% CI)	9.15 [0.49, 169.58]
4 TRM subgrouped by type of radiotherapy	4	2700	Risk Ratio (M-H, Fixed, 95% CI)	2.15 [0.93, 4.95]
4.1 without radiotherapy	1	549	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.26, 2.71]
4.2 with radiotherapy	3	2151	Risk Ratio (M-H, Fixed, 95% CI)	6.13 [1.38, 27.26]

Comparison 4. Analysis of secondary malignancies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Secondary malignancies	5	3332	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.68, 1.48]
2 SM subgrouped by stage of disease	5	3332	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.68, 1.48]
2.1 early unfavourable stage	1	1528	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.45, 1.76]
2.2 advanced stage	4	1804	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.66, 1.70]
3 SM subgrouped by treatment	5	3332	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.68, 1.48]
3.1 only ABVD	4	2605	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.59, 1.61]
3.2 ABVD including regimen	1	727	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.57, 1.92]
4 SM subgrouped by number of cycles of escalated BEACOPP	5	3332	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.68, 1.48]
4.1 eight cycles of escalated BEACOPP	1	727	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.57, 1.92]
4.2 four cycles of escalated BEAOPP	3	1077	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.52, 2.29]
4.3 two cycles of escalated BEACOPP	1	1528	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.45, 1.76]
5 SM subgrouped by type of radiotherapy	5	3332	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.68, 1.48]
5.1 without radiotherapy	1	549	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.50, 3.13]
5.2 with radiotherapy	4	2783	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.62, 1.46]
6 SM subgrouped by length of follow-up	5	3332	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.68, 1.48]
6.1 short-term follow-up (median length up to 5 years)	4	2605	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.59, 1.61]
6.2 long-term follow-up (median length 10 years)	1	727	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.57, 1.92]

Comparison 5. Analysis of AML or MDS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 AML or MDS	5	3332	Risk Ratio (M-H, Fixed, 95% CI)	3.90 [1.36, 11.21]
2 AML/MDS subgrouped by stage of disease	5	3332	Risk Ratio (M-H, Fixed, 95% CI)	3.90 [1.36, 11.21]
2.1 early unfavourable stage	1	1528	Risk Ratio (M-H, Fixed, 95% CI)	5.01 [0.24, 104.25]
2.2 advanced stage	4	1804	Risk Ratio (M-H, Fixed, 95% CI)	3.77 [1.22, 11.64]
3 AML/MDS subgrouped by treatment	5	3332	Risk Ratio (M-H, Fixed, 95% CI)	3.90 [1.36, 11.21]
3.1 only ABVD	4	2605	Risk Ratio (M-H, Fixed, 95% CI)	2.45 [0.71, 8.49]
3.2 ABVD including regimen	1	727	Risk Ratio (M-H, Fixed, 95% CI)	7.84 [1.04, 59.29]
4 AML/MDS subgrouped by number of cycles of escalated BEACOPP	5	3332	Risk Ratio (M-H, Fixed, 95% CI)	3.90 [1.36, 11.21]
4.1 eight cycles of escalated BEACOPP	1	727	Risk Ratio (M-H, Fixed, 95% CI)	7.84 [1.04, 59.29]
4.2 four cycles of escalated BEACOPP	3	1077	Risk Ratio (M-H, Fixed, 95% CI)	2.03 [0.51, 8.05]
4.3 two cycles of escalated BEACOPP	1	1528	Risk Ratio (M-H, Fixed, 95% CI)	5.01 [0.24, 104.25]
5 AML/MDS subgrouped by type of radiotherapy	5	3332	Risk Ratio (M-H, Fixed, 95% CI)	3.90 [1.36, 11.21]
5.1 without radiotherapy	1	549	Risk Ratio (M-H, Fixed, 95% CI)	2.01 [0.37, 10.87]
5.2 with radiotherapy	4	2783	Risk Ratio (M-H, Fixed, 95% CI)	5.27 [1.34, 20.74]
6 AML/MDS subgrouped by length of follow-up	5	3332	Risk Ratio (M-H, Fixed, 95% CI)	3.90 [1.36, 11.21]
6.1 short-term follow-up (median length up to 5 years)	4	2605	Risk Ratio (M-H, Fixed, 95% CI)	2.45 [0.71, 8.49]
6.2 long-term follow-up (median length 10 years)	1	727	Risk Ratio (M-H, Fixed, 95% CI)	7.84 [1.04, 59.29]

Comparison 6. Analysis of fertility

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Secondary amenorrhoea	1	106	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.83, 2.26]

Comparison 7. Analysis of anaemia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Anaemia	3	2425	Risk Ratio (M-H, Fixed, 95% CI)	10.67 [7.14, 15.93]

Comparison 8. Analysis of infection

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Infection	3	2425	Risk Ratio (M-H, Fixed, 95% CI)	3.73 [2.58, 5.38]

Comparison 9. Analysis of neutropenia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Neutropenia	2	519	Risk Ratio (M-H, Fixed, 95% CI)	1.80 [1.52, 2.13]

Comparison 10. Analysis of thrombocytopenia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Thrombocytopenia	3	2425	Risk Ratio (M-H, Fixed, 95% CI)	18.12 [11.77, 27.92]

Comparison 11. Analysis of alopecia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Alopecia	3	2425	Risk Ratio (M-H, Fixed, 95% CI)	1.98 [1.78, 2.21]

Comparison 12. Analysis of constipation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Constipation	2	923	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.56, 2.55]

Comparison 13. Analysis of mucositis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mucositis	3	2425	Risk Ratio (M-H, Fixed, 95% CI)	8.04 [3.72, 17.38]

Comparison 14. Analysis of nausea/vomiting

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Nausea/vomiting	3	2425	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.68, 1.01]

Comparison 15. Analysis of neurologic toxicity

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Neurologic	3	2425	Risk Ratio (M-H, Fixed, 95% CI)	2.04 [1.19, 3.50]

Comparison 16. Analysis of pain

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain	3	2425	Risk Ratio (M-H, Fixed, 95% CI)	2.62 [1.76, 3.90]

Comparison 17. Analysis of respiratory

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Respiratory	3	2549	Risk Ratio (M-H, Fixed, 95% CI)	1.80 [1.01, 3.20]

Comparison 18. Analysis of skin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Skin	2	2227	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.45, 2.34]

Comparison 19. Analysis of heart disease

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 heart	2	1823	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.21, 5.10]

Comparison 20. Analysis of freedom from first progression

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Freedom from first progression	1	331	Hazard Ratio (Fixed, 95% CI)	0.46 [0.27, 0.78]

Comparison 21. Analysis of complete response (CR) rate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 CR	5	3427	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [1.01, 1.06]

Analysis 1.1. Comparison 1 Analysis overall survival, Outcome 1 OS - all - same recruitment period between the 2 arms (HD9).

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 1 Analysis overall survival

Outcome: 1 OS - all - same recruitment period between the 2 arms (HD9)

Analysis 1.2. Comparison 1 Analysis overall survival, Outcome 2 OS subgrouped by stage of disease.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 1 Analysis overall survival

Outcome: 2 OS subgrouped by stage of disease

Analysis 1.3. Comparison 1 Analysis overall survival, Outcome 3 OS subgrouped by treatment.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 1 Analysis overall survival

Outcome: 3 OS subgrouped by treatment

Analysis I.4. Comparison I Analysis overall survival, Outcome 4 OS subgrouped by number of cycles of escalated BEACOPP.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: I Analysis overall survival

Outcome: 4 OS subgrouped by number of cycles of escalated BEACOPP

Analysis 1.5. Comparison 1 Analysis overall survival, Outcome 5 OS subgrouped by length of follow-up.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 1 Analysis overall survival

Outcome: 5 OS subgrouped by length of follow-up

Analysis 1.6. Comparison 1 Analysis overall survival, Outcome 6 OS subgrouped by radiotherapy.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 1 Analysis overall survival

Outcome: 6 OS subgrouped by radiotherapy

Analysis 1.7. Comparison 1 Analysis overall survival, Outcome 7 OS - all recruited patients (HD9) with potential risk of bias due to different time periods of recruitment.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 1 Analysis overall survival

Outcome: 7 OS - all recruited patients (HD9) with potential risk of bias due to different time periods of recruitment

Analysis 2.1. Comparison 2 Analysis of progression-free survival (PFS), Outcome 1 PFS - all - same recruitment period between the 2 arms (HD9).

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 2 Analysis of progression-free survival (PFS)

Outcome: 1 PFS - all - same recruitment period between the 2 arms (HD9)

Analysis 2.2. Comparison 2 Analysis of progression-free survival (PFS), Outcome 2 PFS subgrouped by stage of disease.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 2 Analysis of progression-free survival (PFS)

Outcome: 2 PFS subgrouped by stage of disease

Analysis 2.3. Comparison 2 Analysis of progression-free survival (PFS), Outcome 3 PFS subgrouped by treatment.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 2 Analysis of progression-free survival (PFS)

Outcome: 3 PFS subgrouped by treatment

Analysis 2.4. Comparison 2 Analysis of progression-free survival (PFS), Outcome 4 PFS subgrouped by number of cycles of escalated BEACOPP.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 2 Analysis of progression-free survival (PFS)

Outcome: 4 PFS subgrouped by number of cycles of escalated BEACOPP

Analysis 2.5. Comparison 2 Analysis of progression-free survival (PFS), Outcome 5 PFS subgrouped by length of follow-up.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 2 Analysis of progression-free survival (PFS)

Outcome: 5 PFS subgrouped by length of follow-up

Analysis 2.6. Comparison 2 Analysis of progression-free survival (PFS), Outcome 6 PFS subgrouped by type of radiotherapy.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 2 Analysis of progression-free survival (PFS)

Outcome: 6 PFS subgrouped by type of radiotherapy

Analysis 2.7. Comparison 2 Analysis of progression-free survival (PFS), Outcome 7 PFS - all recruited patients (HD9) with potential risk of bias due to different time periods of recruitment.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 2 Analysis of progression-free survival (PFS)

Outcome: 7 PFS - all recruited patients (HD9) with potential risk of bias due to different time periods of recruitment

Analysis 3.1. Comparison 3 Analysis of treatment-related mortality, Outcome 1 Treatment-related mortality.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 3 Analysis of treatment-related mortality

Outcome: 1 Treatment-related mortality

Analysis 3.2. Comparison 3 Analysis of treatment-related mortality, Outcome 2 TRM subgrouped by stage of disease.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 3 Analysis of treatment-related mortality

Outcome: 2 TRM subgrouped by stage of disease

Analysis 3.3. Comparison 3 Analysis of treatment-related mortality, Outcome 3 TRM subgrouped by number of cycles of escalated BEACOPP.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 3 Analysis of treatment-related mortality

Outcome: 3 TRM subgrouped by number of cycles of escalated BEACOPP

Analysis 3.4. Comparison 3 Analysis of treatment-related mortality, Outcome 4 TRM subgrouped by type of radiotherapy.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 3 Analysis of treatment-related mortality

Outcome: 4 TRM subgrouped by type of radiotherapy

Analysis 4.1. Comparison 4 Analysis of secondary malignancies, Outcome 1 Secondary malignancies.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 4 Analysis of secondary malignancies

Outcome: 1 Secondary malignancies

Analysis 4.2. Comparison 4 Analysis of secondary malignancies, Outcome 2 SM subgrouped by stage of disease.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 4 Analysis of secondary malignancies

Outcome: 2 SM subgrouped by stage of disease

Analysis 4.3. Comparison 4 Analysis of secondary malignancies, Outcome 3 SM subgrouped by treatment.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 4 Analysis of secondary malignancies

Outcome: 3 SM subgrouped by treatment

Analysis 4.4. Comparison 4 Analysis of secondary malignancies, Outcome 4 SM subgrouped by number of cycles of escalated BEACOPP.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 4 Analysis of secondary malignancies

Outcome: 4 SM subgrouped by number of cycles of escalated BEACOPP

Analysis 4.5. Comparison 4 Analysis of secondary malignancies, Outcome 5 SM subgrouped by type of radiotherapy.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 4 Analysis of secondary malignancies

Outcome: 5 SM subgrouped by type of radiotherapy

Analysis 4.6. Comparison 4 Analysis of secondary malignancies, Outcome 6 SM subgrouped by length of follow-up.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 4 Analysis of secondary malignancies

Outcome: 6 SM subgrouped by length of follow-up

Analysis 5.1. Comparison 5 Analysis of AML or MDS, Outcome 1 AML or MDS.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 5 Analysis of AML or MDS

Outcome: 1 AML or MDS

Analysis 5.2. Comparison 5 Analysis of AML or MDS, Outcome 2 AML/MDS subgrouped by stage of disease.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 5 Analysis of AML or MDS

Outcome: 2 AML/MDS subgrouped by stage of disease

Analysis 5.3. Comparison 5 Analysis of AML or MDS, Outcome 3 AML/MDS subgrouped by treatment.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 5 Analysis of AML or MDS

Outcome: 3 AML/MDS subgrouped by treatment

Analysis 5.4. Comparison 5 Analysis of AML or MDS, Outcome 4 AML/MDS subgrouped by number of cycles of escalated BEACOPP.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 5 Analysis of AML or MDS

Outcome: 4 AML/MDS subgrouped by number of cycles of escalated BEACOPP

Analysis 5.5. Comparison 5 Analysis of AML or MDS, Outcome 5 AML/MDS subgrouped by type of radiotherapy.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 5 Analysis of AML or MDS

Outcome: 5 AML/MDS subgrouped by type of radiotherapy

Analysis 5.6. Comparison 5 Analysis of AML or MDS, Outcome 6 AML/MDS subgrouped by length of follow-up.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 5 Analysis of AML or MDS

Outcome: 6 AML/MDS subgrouped by length of follow-up

Analysis 6.1. Comparison 6 Analysis of fertility, Outcome 1 Secondary amenorrhoea.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 6 Analysis of fertility

Outcome: 1 Secondary amenorrhoea

Analysis 7.1. Comparison 7 Analysis of anaemia, Outcome 1 Anaemia.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 7 Analysis of anaemia

Outcome: 1 Anaemia

Analysis 8.1. Comparison 8 Analysis of infection, Outcome 1 Infection.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 8 Analysis of infection

Outcome: 1 Infection

Analysis 9.1. Comparison 9 Analysis of neutropenia, Outcome 1 Neutropenia.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 9 Analysis of neutropenia

Outcome: 1 Neutropenia

Analysis 10.1. Comparison 10 Analysis of thrombocytopenia, Outcome 1 Thrombocytopenia.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 10 Analysis of thrombocytopenia

Outcome: 1 Thrombocytopenia

Analysis 11.1. Comparison 11 Analysis of alopecia, Outcome 1 Alopecia.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 11 Analysis of alopecia

Outcome: 1 Alopecia

Analysis 12.1. Comparison 12 Analysis of constipation, Outcome 1 Constipation.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 12 Analysis of constipation

Outcome: 1 Constipation

Analysis 13.1. Comparison 13 Analysis of mucositis, Outcome 1 Mucositis.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 13 Analysis of mucositis

Outcome: 1 Mucositis

Analysis 14.1. Comparison 14 Analysis of nausea/vomiting, Outcome 1 Nausea/vomiting.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 14 Analysis of nausea/vomiting

Outcome: 1 Nausea/vomiting

Analysis 15.1. Comparison 15 Analysis of neurologic toxicity, Outcome 1 Neurologic.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 15 Analysis of neurologic toxicity

Outcome: 1 Neurologic

Analysis 16.1. Comparison 16 Analysis of pain, Outcome 1 Pain.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 16 Analysis of pain

Outcome: 1 Pain

Analysis 17.1. Comparison 17 Analysis of respiratory, Outcome 1 Respiratory.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 17 Analysis of respiratory

Outcome: 1 Respiratory

Analysis 18.1. Comparison 18 Analysis of skin, Outcome 1 Skin.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 18 Analysis of skin

Outcome: 1 Skin

Analysis 19.1. Comparison 19 Analysis of heart disease, Outcome 1 heart.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 19 Analysis of heart disease

Outcome: 1 heart

Analysis 20.1. Comparison 20 Analysis of freedom from first progression, Outcome 1 Freedom from first progression.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 20 Analysis of freedom from first progression

Outcome: 1 Freedom from first progression

Analysis 21.1. Comparison 21 Analysis of complete response (CR) rate, Outcome 1 CR.

Review: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma

Comparison: 21 Analysis of complete response (CR) rate

Outcome: 1 CR

ADDITIONAL TABLES

Table 1. The escalated BEACOPP regimen

Drug	Single Dose (mg/m ²)	Route	Days given*
Bleomycin	10	IV	8
Etoposide	200	IV	1 to 3
Doxorubicin	35	IV	1
Cyclophosphamide	1200	IV	1
Vincristine	1.4	IV	8
Procarbazine	100	P.O.	1 to 7
Prednisone	40	P.O.	1 to 14

Table 1. The escalated BEACOPP regimen (Continued)

G-CSF		SC	from day 8	
*the regimen was repeated on day 22 IV: intravenously, P.O.: orally, SC: subcutaneous				*the regimen was repeated on day 22 IV: intravenously, P.O.: orally, SC: subcutaneous

Table 2. Adverse events (reported by two trials)

Name of trial	Adverse event	Experimental arm (N)	Control arm (N)
GHSG HD14	Gastrointestinal, others	43/744	14/757
	Urogenital tract	0/744	2/757
	Drug fever	17/744	6/757
	Allergy	12/744	2/757
GSM-HD 2008	Gastrointestinal, others	9/156	3/166
	Fever of unknown reason	2/156	1/166
	Others	16/156	1/166

APPENDICES

Appendix I. MEDLINE search strategy (from 1985 to August 2008)

1. Lymphoma/
2. exp Hodgkin Disease/
3. Germinoblastom\$.tw,kf,ot.
4. Reticulolymphosarcom\$.tw,kf,ot.
5. Hodgkin\$.tw,kf,ot.
6. (malignan\$ adj2 (lymphogranulom\$ or granulom\$)).tw,kf,ot.
7. or/1-6
8. beacopp\$.tw,kf,ot,nm.
9. beacopp protocol.nm.
10. or/8-9
11. Doxorubicin/ or (doxorubi?in\$ or adriamycin\$).tw,kf,ot,nm.
12. Bleomycin/ or bleomy?in\$.tw,kf,ot,nm.
13. Etoposide/ or etoposid\$.tw,kf,ot,nm.
14. Cyclophosphamide/ or (cyclophosphamid\$ or cyclofosamid\$).tw,kf,ot,nm.
15. Procarbazine/ or procarba##n\$.tw,kf,ot,nm.
16. Vincristine/ or (vincristin\$ or onocovin\$).tw,kf,ot,nm.

17. Prednisone/ or predniso\$.tw,kf,ot,nm.
18. and/11-17
19. 10 or 18
20. 7 and 19

Appendix 2. Embase search strategy (from 1985 to August 2008)

1. Lymphoma/
2. exp Hodgkin Disease/
3. Germinoblastom\$.tw.
4. Reticulolymphosarcom\$.tw.
5. Hodgkin\$.tw.
6. (malignan\$ adj2 (lymphogranulom\$ or granulom\$)).tw.
7. or/1-6
8. beacopp\$.tw.
9. beacopp protocol\$.tw.
10. or/8-9
11. Doxorubicin/ or (doxorubi?in\$ or adriamycin\$).tw.
12. Bleomycin/ or bleomy?in\$.tw.
13. Etoposide/ or etoposid\$.tw.
14. Cyclophosphamide/ or (cyclophosphamid\$ or cyclofosfamid\$).tw.
15. Procarbazine/ or procarba##n\$.tw.
16. Vincristine/ or (vincristin\$ or onocovin\$).tw.
17. Prednisone/ or predniso\$.tw.
18. and/11-17
19. 10 or 18
20. 7 and 19

Appendix 3. CENTRAL search strategy (from 1990 to August 2008)

1. MeSH descriptor Lymphoma explode all trees
2. MeSH descriptor Hodgkin Disease explode all trees
3. Germinoblastom* in All Text
4. Reticulolymphosarcom* in All Text
5. Hodgkin* in All Text
6. (malignan* in All Text near/2 lymphogranulom* in All Text)
7. (malignan* in All Text near/2 granulom* in All Text)
8. (#1 or #2 or #3 or #4 or #5 or #6 or #7)
9. MeSH descriptor Doxorubicin explode all trees
10. (doxorubi*in* in All Text or adriamycin* in All Text)
11. MeSH descriptor Bleomycin explode all trees
12. bleomy*in* in All Text
13. MeSH descriptor Etoposide explode all trees
14. etoposid* in All Text
15. MeSH descriptor Cyclophosphamide explode all trees
16. (cyclophosphamid* in All Text or cyclofosfamid* in All Text)
17. MeSH descriptor Vincristine explode all trees
18. (vincristin* in All Text or onocovin* in All Text)
19. MeSH descriptor Procarbazine explode all trees
20. procarba* in All Text
21. MeSH descriptor Prednisone explode all trees
22. predniso* in All Text

23. (#9 or #10)
24. (#11 or #12)
25. (#13 or #14)
26. (#15 or #16)
27. (#17 or #18)
28. (#19 or #20)
29. (#21 or #22)
30. (#23 and #24 and #25 and #26 and #27 and #28 and #29)
31. beacopp* in All Text
32. (#30 or #31)
33. (#8 and #32)

Appendix 4. MEDLINE updated search strategy (from Aug 2008 to Aug 2010)

1. MeSH descriptor Lymphoma explode all trees
2. MeSH descriptor Hodgkin Disease explode all trees
3. Germinoblastom*
4. Reticulolymphosarcom*
5. Hodgkin*
6. (malignan* NEAR/2 lymphogranulom*) or (malignan* NEAR/2 granulom*)
7. (#1 OR #2 OR #3 OR #4 OR #5 OR #6)
8. beacopp*
9. beacopp protocol*
10. ¬(#8 OR #9)
11. ¬MeSH descriptor Doxorubicin explode all trees
12. ¬doxorubi*in*
13. ¬(adriamycin* or adriablastin*)
14. ¬hydroxydaunorubincin*
15. ¬(doxo cell or doxo-cell or dox sl or dox-sl)
16. ¬(doxotec* or doxolem* or doxil*)
17. ¬(rubex* or ribodox* or onkodox*)
18. ¬(myeocet* or caelyx*)
19. Farmiblastin*
20. (#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19)
21. MeSH descriptor Bleomycin explode all trees
22. bleomy*in*
23. bleomicin*
24. (blenoxan* or blanozan* or bleolem*)
25. (bleo cell or bleocell)
26. (#21 OR #22 OR #23 OR #24 OR #25)
27. MeSH descriptor Etoposide explode all trees
28. etoposid*
29. (eposid* or etomedac* or etopophos* or eposin* or etopos*)
30. (eto-gry or exitop* or lastet* or toposar* or celltop*)
31. (vepesid* or onkoposid* or riboposid*)
32. (#27 OR #28 OR #29 OR #30 OR #31)
33. MeSH descriptor Cyclophosphamide explode all trees
34. (cyclophosphamid* or cyclofosamid* or ciclofosamid* or cytophosphan* or cyclophosphan*)
35. (cyclophosphamid* or cyclofosamid* or ciclofosamid* or cytophosphan* or cyclophosphan* or citofosfan*)
36. (b-518 or b518)
37. (cytoxan* or citoxan* or endoxan* or sendoxan* or procytox* or genuxal*)
38. (neosar* or revimmune*)#

39. (#33 OR #34 OR #35 OR #36 OR #37 OR #38)
40. MeSH descriptor Procarbazine explode all trees
41. procarba*
42. (matulan* or natulan* or indicarb*)
43. (#40 OR #41 OR #42)
44. MeSH descriptor Vincristine explode all trees
45. (vincristin* or vintec* or vincrisul* or vincasar*)
46. (oncovin* or onkocristin* or cellcristin* or citom*d* or farmistin* or leurocristin*)
47. (#44 OR #45 OR #46)
48. MeSH descriptor Prednisone explode all trees
49. predniso*
50. (winpred*) or (sterapred*) or (prednidib*) or (predniment* pronisone*)
51. (cartancyl* or cortan* or kortancyl* or encorton* or enkortolon* or decortisyl* orrectodelt*)
52. (panafcort* or panasol* or meticorten* or dacortin* or orason* or cutason*)
53. (#48 OR #49 OR #50 OR #51 OR #52)
54. (#20 AND #26 AND #32 AND #39 AND #43 AND #47 AND #53)
55. (#10 OR #54)
56. (#7 AND #55)
57. (#56), from 2008 to 2010

Appendix 5. CENTRAL updated search strategy (from Aug 2008 to Aug 2010)

1. Lymphoma/
2. exp Hodgkin Disease/
3. Germinoblastom\$.tw,kf,ot.
4. Reticulolymphosarcom\$.tw,kf,ot.
5. Hodgkin\$.tw,kf,ot.
6. (malignan\$ adj2 (lymphogranulom\$ or granulom\$)).tw,kf,ot.
7. or/1-6
8. beacopp\$.tw,kf,ot,nm.
9. beacopp protocol.nm.
10. or/8-9
11. exp Doxorubicin/
12. doxorubi?in\$.tw,kf,ot,nm.
13. (adriamycin\$ or adriablastin\$).tw,kf,ot.
14. hydroxydaunorubicin\$.tw,kf,ot.
15. (doxo cell or doxo-cell or dox sl or dox-sl).tw,kf,ot.
16. (doxotec\$ or doxolem\$ or doxil\$).tw,kf,ot.
17. (rubex\$ or ribodox\$ or onkodox\$).tw,kf,ot.
18. (myeocet\$ or caelyx\$).tw,kf,ot.
19. Farmiblastin\$.tw,kf,ot.
20. or/11-19
21. exp Bleomycin/
22. bleomy?in\$.tw,kf,ot,nm.
23. bleomicin\$.tw,kf,ot.
24. (blenoxan\$ or blanozan\$ or bleolem\$).tw,kf,ot.
25. (bleo cell or bleocell).tw,kf,ot.
26. or/21-25
27. Etoposide/
28. etoposid\$.tw,kf,ot,nm.
29. (eposid\$ or etomedac\$ or etopophos\$ or eposin\$ or etopos).tw,kf,ot.
30. (eto-gry or exitop\$ or lastet\$ or toposar\$ or celltop\$).tw,kf,ot.

31. (vepesid\$ or onkoposid\$ or riboposid\$).tw,kf,ot.
32. or/27-31
33. exp Cyclophosphamide/
34. (cyclophosphamid\$ or cyclofosamid\$ or ciclofosamid\$ or cytophosphan\$ or cyclophosphan\$).tw,kf,ot,nm.
35. (cyclophosphamid\$ or cyclofosamid\$ or ciclofosamid\$ or cytophosphan\$ or cyclophosphan\$ or citofosfan\$).tw,kf,ot,nm.
36. (b-518 or b518).tw,kf,ot,nm.
37. (cytoxan\$ or citoxan\$ or endoxan\$ or sendoxan\$ or procytox\$ or genuxal\$).tw,kf,ot.
38. (neosar\$ or revimmune\$).tw,kf,ot.
39. or/33-38
40. Procarbazine/
41. procarba##n\$.tw,kf,ot,nm.
42. (matulan\$ or natulan\$ or indicarb\$).tw,kf,ot.
43. or/40-42
44. Vincristine/
45. (vincristin\$ or vintec\$ or vincrisul\$ or vincasar\$).tw,kf,ot,nm.
46. (oncovin\$ or onkocristin\$).tw,kf,ot.
47. (cellcristin\$ or citom#d\$ or farmistin\$ or leurocristin\$).tw,kf,ot.
48. or/44-47
49. Prednisone/
50. predniso\$.tw,kf,ot,nm.
51. (winpred\$ or sterapred\$ or prednidib\$ or predniment\$ pronisone\$).tw,kf,ot.
52. (cartancyl\$ or cortan\$ or kortancyl\$ or encorton\$ or enkortolon\$ or decortisyl\$ or rectodelt\$).tw,kf,ot.
53. (panafcort\$ or panasol\$ or meticorten\$ or dacortin\$ or orason\$ or cutason\$).tw,kf,ot.
54. or/49-53
55. 20 and 26 and 32 and 39 and 43 and 48 and 54
56. 10 or 55
57. 56 and 7
58. limit 57 to ed=20081128-20100407
59. from 58 keep 1-25

Appendix 6. MEDLINE updated search strategy (from Nov 2008 to Aug 2016)

1.	Lymphoma/		
2.	exp Hodgkin Disease/		
3.	Germinoblastom\$.tw,kf,ot.		
4.	Reticulolymphosarcom\$.tw,kf,ot.		
5.	Hodgkin\$.tw,kf,ot.		
6.	(malignan\$ adj2 (lymphogranulom\$ or granulom\$)).tw,kf,ot.		
7.	or/1-6		
8.	beacopp\$.tw,kf,ot,nm.		

(Continued)

9.	exp Doxorubicin/		
10.	doxorubi?in\$.tw,kf,ot,nm.		
11.	(adriamycin\$ or adriablastin\$).tw,kf,ot.		
12.	hydroxydaunorubicin\$.tw,kf,ot.		
13.	(doxo cell or doxo-cell or dox sl or dox-sl).tw,kf,ot.		
14.	(doxotec\$ or doxolem\$ or doxil\$).tw,kf,ot.		
15.	(rubex\$ or ribodox\$ or onkodox\$).tw,kf,ot.		
16.	(myeocet\$ or caelyx\$).tw,kf,ot.		
17.	Farmiblastin\$.tw,kf,ot.		
18.	or/9-17		
19.	exp Bleomycin/		
20.	bleomy?in\$.tw,kf,ot,nm.		
21.	bleomicin\$.tw,kf,ot.		
22.	(blenoxan\$ or blanoxan\$ or bleolem\$).tw,kf,ot.		
23.	(bleo cell or bleocell).tw,kf,ot.		
24.	or/19-23		
25.	Etoposide/		
26.	etoposid\$.tw,kf,ot,nm.		
27.	(eposid\$ or etomedac\$ or etopophos\$ or eposin\$ or etopos).tw,kf,ot		
28.	(eto-gry or exitop\$ or lastet\$ or toposar\$ or celltop\$).tw,kf,ot		
29.	(vepesid\$ or onkoposid\$ or riboposid\$).tw,kf,ot.		

(Continued)

30.	or/25-29		
31.	exp Cyclophosphamide/		
32.	(cyclophosphamid\$ or cyclofosfamid\$ or ciclofosfamid\$ or cytophosphan\$ or cyclophosphan\$ or citofosfan\$).tw,kf,ot,nm		
33.	(b-518 or b518).tw,kf,ot,nm.		
34.	(cytoxan\$ or citoxan\$ or endoxan\$ or sendoxan\$ or procytox\$ or genuxal\$).tw,kf,ot		
35.	(neosar\$ or revimmune\$).tw,kf,ot.		
36.	or/31-35		
37.	Procarbazine/		
38.	procarba##n\$.tw,kf,ot,nm.		
39.	(matulan\$ or natulan\$ or indicarb\$).tw,kf,ot.		
40.	or/37-39		
41.	Vincristine/		
42.	(vincristin\$ or vintec\$ or vincrisul\$ or vincasar\$).tw,kf,ot,nm		
43.	(oncovin\$ or onkocristin\$).tw,kf,ot.		
44.	(cellcristin\$ or citom#d\$ or farmistin\$ or leurocristin\$).tw,kf,ot		
45.	or/41-44		
46.	Prednisone/		
47.	predniso\$.tw,kf,ot,nm.		
48.	(winpred\$ or sterapred\$ or prednidib\$ or predniment\$ pronisone\$).tw,kf,ot		

(Continued)

49.	(cartancyl\$ or cortan\$ or kortancyl\$ or encorton\$ or enkortolon\$ or decortisyl\$ or rectodelt\$).tw,kf,ot		
50.	(panafcort\$ or panasol\$ or meticorten\$ or dacortin\$ or orason\$ or cutason\$).tw,kf,ot		
51.	or/46-50		
52.	18 or 24 or 30 or 36 or 40 or 45 or 51		
53.	8 or 52		
54.	53 and 7		
55.	limit 54 to ed=20100401-20100908		
56.	limit 54 to ed=20100901-20101025		
57.	limit 54 to ed=20100401-20100801		
58.	limit 54 to ed=20100801-20111105		
59.	limit 54 to ed=20111105-20130729		
60.	limit 54 to ed=20130729-20140605		
61.	limit 54 to ed=20140605-20151103		
62.	limit 54 to ed=20140605-20151123		
63.	limit 54 to ed=20151123-20160802		

Appendix 7. CENTRAL updated search strategy (from 2008 to Aug 2016)

1. MESH DESCRIPTOR Lymphoma EXPLODE ALL TREES
2. MESH DESCRIPTOR Hodgkin Disease EXPLODE ALL TREES
3. Germinoblastom*:TI,AB,KY
4. Reticulolymphosarcom*:TI,AB,KY
5. ((hodgkin* or hogkin* or hodkin* or hodgin*)):TI,AB,KY
6. ((malignan* near/2 lymphogranulom*) OR (malignan* near/2 granulom*)):TI,AB,KY
7. #1 or #2 or #3 or #4 or #5 or #6
8. beacopp*:TI,AB,KY
9. (beacopp protocol*):TI,AB,KY
10. #8 or #9
11. MESH DESCRIPTOR Doxorubicin EXPLODE ALL TREES
12. doxorubi*in*:TI,AB,KY
13. ((adriamycin* or adriablastin*)):TI,AB,KY

14. hydroxydaunorubicin*:TI,AB,KY
15. ((doxo cell or doxo-cell or dox sl or dox-sl)):TI,AB,KY
16. ((doxotec* or doxolem* or doxil*)):TI,AB,KY
17. ((rubex* or ribodox* or onkodox*)):TI,AB,KY
18. ((myeocet* or caelyx*)):TI,AB,KY
19. Farmiblastin*:TI,AB,KY
20. #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19
21. MESH DESCRIPTOR Bleomycin EXPLODE ALL TREES
22. bleomy*in*:TI,AB,KY
23. bleomicin*:TI,AB,KY
24. ((blenoxan* or blanoxan* or bleolem*)):TI,AB,KY
25. ((bleo cell or bleocell)):TI,AB,KY
26. #21 or #22 or #23 or #24 or #25
27. MESH DESCRIPTOR Etoposide EXPLODE ALL TREES
28. etoposid*:TI,AB,KY
29. ((eposid* or etomedac* or etopophos* or eposin* or etopos*)):TI,AB,KY
30. ((eto-gry or exitop* or lastet* or toposar* or celltop*)):TI,AB,KY
31. ((vepesid* or onkoposid* or riboposid*)):TI,AB,KY
32. #27 or #28 or #29 or #30 or #31
33. MESH DESCRIPTOR Cyclophosphamide EXPLODE ALL TREES
34. ((cyclophosphamid* or cyclofosamid* or ciclofosamid* or cytophosphan* or cyclophosphan* or citofosfan*)):TI,AB,KY
35. ((b-518 or b518)):TI,AB,KY
36. ((cytoxan* or citoxan* or endoxan* or sendoxan* or procytos* or genuxal*)):TI,AB,KY
37. ((neosar* or revimmune*)):TI,AB,KY
38. #33 or #34 or #35 or #36 or #37
39. MESH DESCRIPTOR Procarbazine EXPLODE ALL TREES
40. procarba*:TI,AB,KY
41. ((matulan* or natulan* or indicarb*)):TI,AB,KY
42. #39 or #40 or #41
43. MESH DESCRIPTOR Vincristine EXPLODE ALL TREES
44. ((vincristin* or vintec* or vincrisul* or vincasar*)):TI,AB,KY
45. ((oncovin* or onkocristin* or cellcristin* or citom*d* or farmistin* or leurocristin*)):TI,AB,KY
46. #43 or #44 or #45
47. MESH DESCRIPTOR Prednisone EXPLODE ALL TREES
48. predniso*:TI,AB,KY
49. (winpred* OR sterapred* OR prednidib* OR predniment* pronisone*):TI,AB,KY
50. ((cartancyl* or cortan* or kortancyl* or encorton* or enkortolon* or decortisyl* orrectodelt*)):TI,AB,KY
51. ((panafcort* or panasol* or meticorten* or dacortin* or orason* or cutason*)):TI,AB,KY
52. #47 or #48 or #49 or #50 or #51
53. #20 and #26 and #32 and #38 and #42 and #48 and #52
54. #10 or #53
55. #7 and #54

WHAT'S NEW

Last assessed as up-to-date: 17 March 2017.

Date	Event	Description
17 March 2017	New citation required and conclusions have changed	New trial included leading to the evidence of a difference in overall survival
17 March 2017	New search has been performed	New search, one additional trial included

CONTRIBUTIONS OF AUTHORS

AW: data extraction.

IM: development of the search strategy.

AE: clinical expertise.

CB: conception of the primary review, writing of the protocol, data extraction in the primary and updated review, statistical expertise, grant application for the primary review.

BT: clinical expertise.

NS: data extraction, methodological expertise, writing updated review

All authors have read and accepted the final version of the updated review.

DECLARATIONS OF INTEREST

AW: none known

IM: none known

CB: none known

AE is chairman of the German Hodgkin Study Group and conducted two of the five included studies ([GHSG HD9](#); [GHSG HD14](#)).

BT is study physician of the GHSG and was sub-investigator in [GHSG HD14](#).

NS: none known

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- This review was funded by the Federal Ministry of Education and Research, Germany.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We searched more trial registries than mentioned in the previous version to identify all ongoing and completed trials in this field.

We restricted subgroup and sensitivity analyses to the outcomes reported in the 'Summary of findings' table, to provide clinically meaningful results.

In the 'Summary of findings' table we replaced the endpoint complete response rate by quality of life which we consider a more patient-relevant outcome.

NOTES

Some passages in this review, especially in the methods part, are from the standard template of the Cochrane Haematological Malignancies Review Group.

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Combined Chemotherapy Protocols [administration & dosage; * therapeutic use]; Bleomycin [administration & dosage]; Cyclophosphamide [administration & dosage]; Dacarbazine [administration & dosage]; Doxorubicin [administration & dosage]; Etoposide [administration & dosage]; Hodgkin Disease [* drug therapy; pathology]; Prednisone [administration & dosage]; Procarbazine [administration & dosage]; Randomized Controlled Trials as Topic; Vinblastine [administration & dosage]; Vincristine [administration & dosage]

MeSH check words

Adolescent; Adult; Humans; Middle Aged; Young Adult