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[Intervention Review]

Granulopoiesis-stimulating factors to prevent adverse effects in the treatment of malignant lymphoma

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ABSTRACT

Background

Granulopoiesis-stimulating factors, such as granulocyte-colony-stimulating factor (G-CSF) and granulocyte-macrophage-colony-stimulating factor (GM-CSF), are being used to prevent febrile neutropenia and infection in patients undergoing treatment for malignant lymphoma. The question of whether G-CSF and GM-CSF improve dose intensity, tumour response, and overall survival in this patient population has not been answered yet. Since the results from single studies are inconclusive, a systematic review was undertaken.

Objectives

To determine the effectiveness of G-CSF and GM-CSF in patients with malignant lymphoma with respect to preventing neutropenia, febrile neutropenia and infection; improving quality of life, adherence to treatment protocol, tumour response, freedom from treatment failure (FFTF) and overall survival (OS); and adverse effects.

Search methods

We searched The Cochrane Library, MEDLINE, EMBASE, CancerLit, and other relevant literature databases; Internet databases of ongoing trials; and conference proceedings of the American Society of Clinical Oncology and the American Society of Hematology (1980 - 2007). We included full-text and abstract publications as well as unpublished data.

Selection criteria

Randomised controlled trials comparing prophylaxis with G-CSF or GM-CSF versus placebo/no prophylaxis in adult patients with malignant lymphoma undergoing chemotherapy were included for review. Both study arms had to receive identical chemotherapy and supportive care.

Data collection and analysis

Trial eligibility and quality assessment, data extraction and analysis were done by two reviewers independently. Authors were contacted to obtain missing data.

Main results

We included 13 eligible randomised controlled trials with 2607 randomised patients. Compared with no prophylaxis, both G-CSF and GM-CSF did not improve overall survival (hazard ratio 0.97; 95% CI 0.87 to 1.09) or FFTF (hazard ratio 1.11; 95% CI 0.91 to 1.35). Prophylaxis

significantly reduced the relative risk (RR) for severe neutropenia (RR 0.67; 95% confidence interval (CI) 0.60 to 0.73), febrile neutropenia (RR 0.74; 95% CI 0.62 to 0.89) and infection (RR 0.74; 95% CI 0.64 to 0.85). There was no evidence that either G-CSF or GM-CSF reduced the number of patients requiring intravenous antibiotics (RR 0.82; 95%CI 0.57 to 1.18); lowered infection related mortality (RR 0.93; 95% CI 0.51 to 1.71); or improved complete tumour response (RR 1.03; 95% CI 0.95 to 1.10).One study evaluated quality of life parameters and found no differences between the treatment groups.

Authors' conclusions

G-CSF and GM-CSF, when used as a prophylaxis in patients with malignant lymphoma undergoing conventional chemotherapy, reduce the risk of neutropenia, febrile neutropenia and infection. However, based on the randomised trials currently available, there is no evidence that either G-CSF or GM-CSF provide a significant advantage in terms of complete tumour response, FFTF or OS.

PLAIN LANGUAGE SUMMARY

Granulopoiesis-stimulating factors in the prevention of adverse effects during the therapeutic treatment of malignant lymphoma.

Lymphoma is a cancer that begins in the lymph nodes. It can be treated with chemotherapy (anti-cancer drugs), but this disrupts the immune system and lowers white cell counts. This can increase a person's risk of infection and limit the amount of chemotherapy that can be given. Granulopoiesis-stimulating factors (GSF) can increase the body's production of white cells. The review found that treatment with GSF increases white cell counts and reduces the risk of infection in people receiving chemotherapy for lymphoma. However, GSF treatment did not improve survival. More research is needed to improve GSF treatments.

BACKGROUND

Description of the condition

Malignant lymphomas are a heterogeneous group of neoplastic disorders that develop in lymphatic cells (Freedman 1999). These tumours usually originate in lymph nodes and spread along the lymphatic system, involving lymphatic tissues such as lymph nodes and the spleen. Malignant cells can also infiltrate non-lymphatic tissues such as bone, liver, lung and, less frequently, skin and brain, either by haematogenesis or by invasion of adjacent tumour masses. Based on their distinct histology, malignant lymphomas are classified as Hodgkin's disease (HD) or non-Hodgkin's lymphoma (NHL). The incidence of HD is steady, affecting 3 people out of every 100,000 per year in Europe and Northern America, whereas the incidence of NHL has increased in recent years. Nowadays 14 people in 100,000 are affected by NHL every year (Engert 1994). The aetiology of malignant lymphoma remains unclear. An association with viral infections, such as Epstein-Barr virus, and genetic predisposition are being discussed (Engert 1994; Herrmann 1998). Depending on their histological classification, stage and prognostic factors, malignant lymphomas are treated with chemotherapy, radiotherapy or both.

One limiting factor in the treatment of malignant lymphoma is the myelosuppressive side effect of cytotoxic drugs. Myelosuppression is characterised by leucopenia, anaemia and thrombocytopenia. Neutropenia, neutropenic fever and neutropenia-related infections are dose-limiting events during chemotherapy. The risk of febrile neutropenia and subsequent infection is directly related to the degree and duration of neutropenia (Bodey 1966; Bodey 1986). Febrile neutropenia and neutropenia-related infections can result in longer hospital stays and higher mortality. Consequently, reducing the dose of cytostatic drugs or increasing the interval between treatment courses is often required (Talcott 1992; Klastersky 2000). The Goldie-Coldman hypothesis suggests that the application of the intended dose on time may improve tumour response and overall survival (Goldie 1983). Therefore, reducing the intended dose intensity is clinically undesirable (Hryniuk 1984; Hryniuk 1986; Hryniuk 1987). In this context, malignant lymphomas are of particular interest since they have been shown to be chemosensitive, both in experimental models (Skipper 1990) and in retrospective clinical analyses (DeVita 1987; Armitage 1993; Lepage 1993).

Description of the intervention

Haematopoietic growth factors, such as granulocyte-colony-stimulating factor (G-CSF) and granulocyte-macrophage-colony-stimulating factor (GM-CSF), stimulate haematopoietic progenitors, thereby increasing the number of functional neutrophils (Lopez 1986; Bronchud 1988; Crawford 1991). These drugs were introduced in an attempt to prevent and treat neutropenia, neutropenic fever and neutropenia-related infections. G-CSF predominantly augments the proliferation, maturation and release of neutrophils (Roskos 1998; Dempke 2000), whereas GM-CSF enhances the proliferation and differentiation of macrophages as well (Dempke 2000). The most common side effect of G-CSF is bone pain; other less common side effects are myalgia and elevation of lactate dehydrogenase, uric acid and serum and leucocyte alkaline phosphatase levels. Less frequently, patients may also suffer from exacerbation of pre-existing inflammatory conditions such as psoriasis, vasculitis or eczema. GM-CSF has similar side effects, although injection site reactions are seen more often. Patients also complain of bone pain, myalgia, fever, nausea, fatigue, headache and chills (ASCO Guidelines 1994). Clinical trials indicate that both G-CSF and GM-CSF decrease fever incidence and the incidence and duration of neutropenia after standard chemotherapy (Morstyn 1988; Yoshida 1990; Hovgaard 1992). However, the scant results from prospective, randomised studies directly comparing G-CSF and GM-CSF are inconclusive, and it is unknown which of these agents is superior (Lydaki 1995; Magrath 1997; Beveridge 1998; Deb 1998; Alvarado Ibarra 1999; Bennett 2000a). In a meta-analysis of patients with solid cancers or lymphoma, pegfilgrastim reduced the incidence of febrile neutropenia. However, only 15% of patients had malignant lymphoma (Pinto 2007).

Although G-CSF and GM-CSF are cost intensive drugs, economic evaluations have demonstrated an overall cost reduction from reduced antibiotic use and shorter hospital stays (Bow 1998). However, this economic benefit is achieved only in specific clinical settings, and the controversy over defining economic thresholds continues (Souêtre 1994; Zagonel 1994; Bobey 1998; Lyman 1998; ASCO Guidelines 2000; Bennett 2000b; Lyman 2000; EORTC Guidelines 2006; ASCO Guidelines 2006).

Why it is important to do this review

The considerable uncertainty surrounding the clinical use of these agents led the American Society of Clinical Oncology (ASCO) to set up guidelines in 1994 for the use of G-CSF and GM-CSF in the treatment of both solid and haematological malignancies (updated in 1996, 2000 and 2006) in order to avoid infectious complications and maintain dose intensities. The current ASCO guidelines recommend the primary administration of G-CSF and GM-CSF in clinical settings where the expected risk of suffering febrile neutropenia is at least 20%. This threshold was reduced from 40% in 2005, following the publication of two trials in patients with solid tumours and a risk of febrile neutropenia in the control arm between 19% in one study (Vogel 2005) and 32% with concomitant antibiotic prophylaxis int the other study (Timmer-Bonte 2005). Granulopoiesis-stimulating factors are also recommended for patients who have developed febrile neutropenia in a previous chemotherapy cycle or when the alternative of reducing the chemotherapy dose is not appropriate (secondary prophylaxis). G-CSF and GM-CSF were not recommended as a supportive measure to increase chemotherapy dosages beyond standard regimens outside of a clinical trial (ASCO Guidelines 2006). Systematic reviews on the effectiveness of G-CSF in the chemotherapeutic treatment of solid and haematological malignancies provided evidence that G-CSF reduced the incidence of febrile neutropenia (Rusthoven 1998; Kuderer 2007). However, the relevance of the results with respect to malignant lymphoma are questionable since both reviews only included a limited number of lymphoma trials. For example, the review by Kuderer 2007 only included 5 trials with lymphoma patients (Ösby 2003; Doorduijn 2003; Gisselbrecht 1997; Zinzani 1997; Pettengell 1992), compared to 12 trials published during their search period. Another systematic review assessing the effectiveness of G-CSF and GM-CSF in the treatment of haematological tumours has not been published in full and cannot be assessed in detail (Hackshaw 2004). Therefore, the critical question of whether G-CSF and GM-CSF improve dose intensity, tumour response and overall survival in the treatment of malignant lymphoma remains unanswered.

Since current evidence based information on the use of G-CSF and GM-CSF is inconclusive in a number of key questions and includes only parts of the existing literature, we conducted a comprehensive systematic review. In the first publication of this review we included 11 prospectively randomised studies with a total of 1431 patients, the first update included 12 trials with 1820 patients. We now present the second update, which includes 13 trials with 2604 randomised patients. All patients had either HD or NHL and received standard chemotherapy with or without G-CSF or GM-CSF prophylaxis. The outcome measures examined included overall survival (OS), freedom from treatment failure (FFTF), risk and duration of neutropenia and febrile neutropenia, infection, mortality, received dose intensity, tumour response, adverse events and quality of life.

OBJECTIVES

We conducted a systematic review of randomised controlled trials of patients with malignant lymphoma to determine the effectiveness of G-CSF and GM-CSF in:

1. improving OS and FFTF (primary outcome measures);
2. decreasing the risk and duration of neutropenia and febrile neutropenia, infection and mortality during chemotherapy; improving received dose intensity, tumour response and quality of life (secondary outcome measures). Adverse effects were also assessed.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised controlled trials comparing G-CSF or GM-CSF prophylaxis with placebo/no prophylaxis were included. Studies on long lasting G-CSF preparations such as filgrastim are eligible as well (this inclusion criterion was added in 2008). Crossover studies, quasi-randomised, e.g. treatment allocation alternate or by date of birth, and non-randomised comparative studies were excluded. Studies with less than ten lymphoma patients per study arm were disqualified. Abstracts and unpublished data were included if sufficient information on study design, patient characteristics, interventions and outcomes was available. Otherwise they were excluded or included with reservations.

Types of participants

Eligible patients were older than 16 years and had NHL or HD confirmed by biopsy. The following histological classifications were admitted: Working Formulation, Kiel-, REAL- and WHO-classification. Acute and chronic leukaemias, including chronic lymphatic leukaemia, multiple myeloma and human immunodeficiency virus (HIV) associated lymphoma were excluded because they include disease specific immunodeficiencies that may confound the results.

Types of interventions

G-CSF or GM-CSF had to be given at doses of at least 1 µg/kg/day, intravenously or subcutaneously, as primary prophylaxis during a standard non-myeloablative chemotherapy prior to the onset of neutropenia in the first- or second-line treatment of malignant lymphoma. G-CSF or GM-CSF had to be given within 72 hours of administering cytotoxic substances and in each cycle of chemotherapy. The control group had to receive an identical chemotherapy regimen and, apart from G-CSF or GM-CSF, the same supportive care, e.g. antibiotic prophylaxis, in addition to a placebo or no prophylaxis. Trials investigating the sequential administration of G-CSF or GM-CSF, or their secondary prophylactic administration and therapeutic use in established neutropenia and febrile neutropenia, were excluded, as were trials on myeloablative chemotherapy regimens with consecutive stem cell support.

Types of outcome measures

Primary outcomes

- overall survival;
- freedom from treatment failure.

Secondary outcomes

- quality of life;
- risk and duration of neutropenia;
- risk and duration of febrile neutropenia;
- infection;
- mortality during chemotherapy;
- received dose intensity of chemotherapy;
- tumour response (complete response);
- adverse effects of G-CSF and GM-CSF;
- risk and duration of parenteral antibiotic treatment;
- hospitalisation;
- risk and duration of thrombocytopenia and anaemia.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CancerLit, Medikat, Russmed Articles, SOMED, Toxline, BIOSIS Previews and LILACS. The search covered the time period from January 1980 to April 21 2008. No language restriction was applied. In databases other than CENTRAL, we used the highly sensitive search strategy for identifying reports of randomised controlled trials developed by Dickersin 1994. See Appendix 1 for the MEDLINE search strategy. This search strategy was adapted for use in the other databases.

We also searched internet databases of grey literature (SIGLE) and ongoing trials as follows. These websites were last checked for relevant trials in April 2008.

1. www.controlled-trials.com
2. http://clinicaltrials.nci.nih.gov
3. http://clinicaltrials.gov/ct/gui
4. www.eortc.be/
5. www.ctc.usyd.edu.au/
6. www.trialscentral.org/index.html

Searching other resources

We handsearched the conference proceedings of the American Society of Clinical Oncology (1980 to August 2007) and the American Society of Hematology (1980 to 2007) and two medical journals: American Journal of Hematology and Annals of Hematology. Citations of all trials identified in the search were checked for additional references. We also contacted experts in the

field and pharmaceutical companies (Amgen, Chugai, Novartis Pharma, Janssen-Cilag, Sandoz, Schering-Plough) for additional unpublished or ongoing trials.

Data collection and analysis

Selection of studies

Titles and abstracts of studies identified from the above sources were screened independently by two reviewers (JB, MR, CH) according to the eligibility criteria. If this could not be done satisfactorily from the title and abstract, the full-text was obtained. Studies that met the inclusion criteria were assessed with an eligibility form, which contained the following questions.

1. Is the study described as randomised?
2. Did the participants in the study have malignant lymphoma?
3. Were the participants at risk of febrile neutropenia?
4. Were the participants adults (> 16 years of age)?
5. Was one group (treatment group) given G-CSF or GM-CSF subcutaneously or intravenously (not per os) after the course of chemotherapy in a dose of at least 1 µg/kg/day?
6. Were the groups treated identically (identical chemotherapy and supportive care such as antibiotic prophylaxis) other than for the named intervention?
7. Did the study document dose intensity and tumour response or febrile neutropenia?

Studies had to meet all of the above criteria to be eligible. If there was insufficient information to judge eligibility, the first author of the study or report was contacted for clarification. Any disagreements between the reviewers were resolved by discussion. Any duplicate reports were identified. Full-text versions of all eligible studies were obtained for quality assessment and data extraction.

Data extraction and management

Data on study design, patient characteristics, interventions and outcome were extracted independently by two reviewers (MR, JB and CH) using a previously designed data extraction form that included the following items.

1. General information: title, authors, source, contact address, country, language and year of publication, duplicate publications, sponsors and trial setting.
2. Trial characteristics such as inclusion and exclusion criteria, sample size, diagnostic criteria, assessment of compliance;, method of randomisation, concealment of allocation and blinding of patients, care givers and outcome assessors, withdrawals, losses to follow up and intention-to-treat analysis were extracted separately with a validity form.
3. Interventions: placebo, intervention and co-medication including dose, route and timing.
4. Patients: sample size, disease and baseline characteristics.
5. Outcomes: outcomes as specified above.

Disagreements arising at any stage were resolved by discussion and consensus. All authors were contacted to obtain missing data on study design, characteristics of patients, interventions and primary and selected secondary outcome measures (rate and duration of neutropenia and febrile neutropenia, mortality during and after chemotherapy, complete response, FFTF and OS).

Assessment of risk of bias in included studies

Study quality was assessed independently by two unblinded reviewers (JB, MR, CH). Any disagreements were discussed within the group until consensus was reached. Quality was assessed using an in-house assessment form that has not been validated (sources used: Jadad 1996; Verhagen 1998). The following criteria were considered.

1. Was the randomisation method satisfactory?
2. Was treatment allocation concealed?
3. Were the groups similar at baseline regarding the most important prognostic factors?
4. Was treatment allocation masked from the participants?
5. Was treatment allocation masked from the clinicians?
6. Was treatment allocation masked from the outcome assessors?
7. Was the number of withdrawals, dropouts and losses to follow-up in each group stated?
8. Was an intention-to-treat analysis included in the data analysis?

We defined important prognostic factors as age, gender, performance status, stage of disease, presence of B-symptoms, above normal lactate dehydrogenase concentration, bone marrow involvement and untreated, resistant or relapsed disease. We explored the influence of individual quality criteria in a sensitivity analysis.

Data synthesis

For statistical analysis, we used RevMan 5, R and STATA. To estimate OS and FFTF, hazard ratios (HR) were calculated. If individual patient data were not available we extracted and analysed data from the published survival curves using methods described by Parmar 1998. For binary data, relative risks (RR) and 95% confidence intervals (CI)were calculated for each trial and the Mantel-Haenszel method was used
for pooling. The results were pooled using a fixed effect model.
Number needed to treat and number needed to harm, with corresponding confidence intervals, were calculated for ease of interpretation. Continuous data were calculated as weighted mean differences with 95% CI and summarised, if appropriate. Heterogeneity of treatment effect between trials was tested using a chi squared statistic with significance set at $P < 0.05$. The robustness of the overall results and causes of heterogeneity were assessed by sensitivity and subgroup analyses as described below. In meta-analyses of at least four trials, a funnel plot was generated and a linear regression test (Egger 1997) was performed to examine the presence of bias. A probability value of less than 0.1 was considered significant for the linear regression test. All data included were based on 'intention-to-treat' or 'full set analysis' as defined by ICH 1999. Data based on 'per protocol analysis' were not included.

Subgroup analysis and investigation of heterogeneity

The clinical and methodological diversity of the included studies, as well as the statistical heterogeneity of selected results were analysed according to the following criteria.

1. Type of drug (G-CSF compared to GM-CSF);
2. HD versus NHL;

3. Age (trials restricted to age > 60 years versus trials including all ages);
4. Administration of prophylactic antibiotic drugs during chemotherapy;
5. Different toxicity of chemotherapy regimens: chemotherapies applied in the different studies may differ in their specific haematological toxicity. The haemato-toxicity of different chemotherapy regimens was categorised indirectly by means of the incidence of neutropenia in the control group.

Sensitivity analysis

1. Placebo controlled studies versus open label studies;
2. Concealment of allocation;
3. Size of studies (including less than 100 patients versus at least 100 patients);
4. Published versus unpublished, unreported or abstract based data;
5. Duration of follow-up

RESULTS

Description of studies

The electronic update search from August 2003 to April 2008 retrieved 306 abstracts. Of these 3 were retrieved for an evaluation of the full text and one was included in the updated version of the review.

Please note: previously unreported data and unpublished studies are marked with an asterix (*).

Eligible studies

We identified 16 randomised controlled trials that met our inclusion criteria. Of these trials, three additional follow-up reports (Engelhard 1994; Gerhartz 1994a; Zinzani 1999) and an economic analysis of identical patient data (Souêtre 1994) were identified. Two of the 16 studies were excluded. One study of 100 patients has not been published (Unpublished trial), while the other study was published only as an interim analysis and did not report any useable data (as part of a multicenter trial, N = 14) (Liberati 1991). We were unable to obtain data from the original investigators for either of these studies. In addition, we initially identified three studies that were ongoing (Blay; Cunningham; Doorduijn 2003). Two of these (Cunningham; Doorduijn 2000) were published in the meantime and are included in the present updated review (Doorduijn 2003; Burton 2006).

Included studies

Thirteen randomised studies with a total of 2607 randomised patients were analysed (Cunningham*; Pettengell 1992; Bastion 1993; Gerhartz 1993; Avilés 1994; Fridrik 1997; Gisselbrecht 1997; Zinzani 1997; Dunlop 1998; Aglietta 2000; Doorduijn 2003; Ösby 2003; Burton 2006) (see 'Characteristics of included studies' table). All trials were reported in English. All first authors were contacted to obtain unreported data. We obtained additional information on study design, patient characteristics and selected outcome data for nine trials (Cunningham*; Avilés 1994; Fridrik 1997; Zinzani 1997; Gisselbrecht 1997; Dunlop 1998; Björkholm 1999; Aglietta 2000; Doorduijn 2003).

Eleven studies evaluated G-CSF (Cunningham*; Pettengell 1992; Bastion 1993; Avilés 1994; Fridrik 1997; Gisselbrecht 1997; Zinzani 1997; Dunlop 1998; Doorduijn 2003; Ösby 2003; Burton 2006) and two studies evaluated GM-CSF versus placebo or no treatment (Gerhartz 1993; Aglietta 2000). Two studies were restricted to patients with HD (Dunlop 1998; Aglietta 2000); one study analysed both NHL and HD (Cunningham*) and ten studies included NHL patients only (Pettengell 1992; Bastion 1993; Gerhartz 1993; Avilés 1994; Fridrik 1997; Gisselbrecht 1997; Zinzani 1997; Doorduijn 2003; Ösby 2003; Burton 2006). Twelve studies included newly diagnosed patients only, while one study was conducted in patients with relapsed lymphoma (Cunningham*). Nine of the thirteen studies had a sample population aged between 15 and 77 years, whereas four studies were restricted to patients older than sixty years (Zinzani 1997; Doorduijn 2003; Ösby 2003, Burton 2006).

Growths factors were given before the onset of neutropenia and less than 48 hours after cytotoxic drug administration at doses of 5 µg/kg/day, or in equivalent doses of 230 µg/m^2 (G-CSF) (Pettengell 1992), 300 µg/day (G-CSF) (Doorduijn 2003), 263 µg/day (G-CSF) (Burton 2006) or 400 µg/day (GM-CSF) (Gerhartz 1993), subcutaneously during each course of chemotherapy. In one study, GM-CSF was given between chemotherapy cycles to investigate whether GM-CSF given before chemotherapy is myeloprotective (Aglietta 2000). All chemotherapy regimens applied were CHOP or MOPP-like and were moderately myelosuppressive. Antibiotic prophylaxis was given in three studies (Pettengell 1992; Zinzani 1997; Burton 2006). Withdrawals and dropouts were stated in nine reports (Cunningham*; Pettengell 1992; Gerhartz 1993; Avilés 1994; Fridrik 1997; Gisselbrecht 1997; Dunlop 1998; Aglietta 2000; Doorduijn 2003). In one abstract publication, the specific number of patients in each study arm was not reported but results were reported in percentages (Bastion 1993). Assuming equal group sizes, we distributed the total number of patients (N = 119) at random to the four different study arms. One study was never published but the data were kindly provided by the principal investigator (Cunningham*). One study (Souêtre 1994) presented an economic analysis of patient data that were presented as clinical outcome data elsewhere (Gisselbrecht 1997). In five of the studies, two different chemotherapy regimens with or without G-CSF were analysed in four separate study arms (Bastion 1993; Gisselbrecht 1997; Dunlop 1998; Ösby 2003; Burton 2006), and we analysed the data, where possible, accordingly (Bastion ACVBP 1993; Bastion VIMMM 1993; Dunlop MOPP 1998; Dunlop MOPP/EVAP 98; Ösby CHOP 2003; Ösby CNOP 2003). Only three studies (Zinzani 1997; Doorduijn 2003; Burton 2006) were not sponsored by the pharmaceutical industry.

Excluded studies

Thirty-seven studies did not meet the inclusion criteria. One study in children and adults (Magrath 1996; Adde 1998) and three studies of various tumour entities (Yau 1996; Gregory 1998; Rao 2005) were excluded because there were fewer than ten eligible adult lymphoma patients per study arm. We also excluded ten non-randomised studies (Gianni 1990; Ho 1990; Riccardi 1993; Zagonel 1994; Mangiagalli 1995; Niitsu 1995; Bertini 1996; Gustavsson 1997; Wilson 1998; Gordon 1999) and three crossover studies (Motoyoshi 1986; Shi 1994; Shi 1996). Two trials dealing with the secondary prevention of febrile neutropenia (Kaku 1993; Maiche 1993), two studies on the treatment of chemotherapy induced neutropenia (Gerhartz 1993; Hartmann 1997) and seven trials on the treatment of established febrile neutropenia (Bodey 1994; Maher 1994;

Mayordomo 1995; Anaissie 1996; Vellenga 1996; Yoshida 1999; Lopez-Hernandez 2000) were also excluded. Additionally, we discarded one trial on HIV-associated lymphoma (Kaplan 1991) and two trials investigating patients with multiple myeloma exclusively (Moreau 1997; Togawa 2000). Two further studies were excluded because patients received GM-CSF or placebo only in the first two cycles of chemotherapy (Bergmann 1995) or received G-CSF only prior to the first cycle of chemotherapy (Hansen 1995). We excluded one study where G-CSF administration did not start before the completion of the second cycle of chemotherapy (Ogawa 1990; Kaneko 1991) and one trial on the topical administration of G-CSF for the prevention of mucositis (Karthaus 1998). Two dose finding studies were also excluded (Hovgaard 1992; Seymour 1995).

Risk of bias in included studies

All trials were described as randomised. In ten of thirteen trials, adequate measures were taken to conceal treatment allocation (Cunningham*; Gerhartz 1993; Avilés 1994; Fridrik 1997; Gisselbrecht 1997; Zinzani 1997; Dunlop 1998; Aglietta 2000; Ösby 2003; Doorduijn 2003). In three studies, the concealment of allocation could not be clarified (Pettengell 1992; Bastion 1993; Burton 2006). At baseline, the distribution of prognostic factors, such as age and stage of disease, was well balanced in the study groups. Five trials were placebo-controlled (Bastion 1993; Gerhartz 1993; Avilés 1994; Gisselbrecht 1997; Aglietta 2000). Nine studies included intention-to-treat calculations in the analysis of primary outcomes (Cunningham*; Pettengell 1992; Avilés 1994; Gisselbrecht 1997; Dunlop MOPP 1998; Aglietta 2000; Ösby 2003; Doorduijn 2003; Burton 2006). Withdrawals and losses to follow up were stated in nine out of eleven published trials (full text) (Pettengell 1992; Gerhartz 1993; Avilés 1994; Fridrik 1997; Gisselbrecht 1997; Dunlop 1998; Aglietta 2000; Doorduijn 2003; Ösby 2003). In two reports, the number of withdrawals was stated but the reasons were not given (Fridrik 1997; Gisselbrecht 1997). For details of the quality assessment see Table 1.

Effects of interventions

As described above, trials that examined two chemotherapy regimens with or without G-CSF were analysed according to the chemotherapy regimen. For this reason the true number of included studies may be lower than the number of studies calculated by RevMan automatically in the table of outcomes.

Primary outcome measures

Overall survival

Ten studies including 2221 patients were analysed (Cunningham*; Pettengell 1992; Engelhard 1994; Fridrik 1997; Zinzani 1997; Dunlop 1998; Björkholm 1999; Aglietta 2000; Doorduijn 2003; Burton 2006). Dunlop 1998 was analysed according to the chemotherapy regimen (Dunlop MOPP 1998* ; Dunlop MOPP/EVAP 98*). Aglietta 2000 only provided data for 29 of 56 patients with complete patient records (see Figure 1). The pooled HR was 0.97 (95% CI 0.87 to 1.09). There was no significant statistical heterogeneity among the trials (chi squared = 4.59, df = 10, P = 0.92). The average observation time of the studies was 4.3 years, range 1.3 to 7.9. Sensitivity analyses (see comparison 2) did not show any significant differences with respect to type of growth factor, tumour entity, age of patients, antibiotic prophylaxis, quality and size of study or length of follow-up. Based on the data available, there is no evidence that either G-CSF or GM-CSF improve OS (Figure 2; Figure 3; Figure 4; Figure 5; Figure 6; Figure 7; Figure 8; Figure 9).

Figure 1. Forest plot of comparison: 1 G-CSF/GM-CSF versus control, outcome: 1.1 Overall survival.

Study or Subgroup	G-/GM-CSF Events	Total	Control Events	Total	O-E	Variance	Weight	Peto Odds Ratio Exp[(O-E) / V], Fixed, 95% CI
Aglietta 2000*	1	17	2	12	-0.81	0.73	0.3%	0.33 [0.03, 3.27]
Björkholm 1999	141	226	150	229	-7.22	68.53	24.6%	0.90 [0.71, 1.14]
Burton 2006	200	387	219	397	-7.57	104.73	37.6%	0.93 [0.77, 1.13]
Cunningham*	14	18	16	21	0.9	7.36	2.6%	1.13 [0.55, 2.33]
Doorduijn 2003	123	197	123	192	2.43	61.5	22.1%	1.04 [0.81, 1.34]
Dunlop MOPP 1998*	3	13	4	12	-0.79	1.75	0.6%	0.64 [0.14, 2.80]
Dunlop MOPP/EVAP 98*	6	14	3	11	1.58	2.22	0.8%	2.04 [0.55, 7.59]
Engelhard 1994	22	87	15	85	2.47	8.59	3.1%	1.33 [0.68, 2.60]
Fridrik 1997*	14	38	12	36	0.4	6.5	2.3%	1.06 [0.49, 2.29]
Pettengell 1992	11	41	12	39	0.98	5.75	2.1%	1.19 [0.52, 2.69]
Zinzani 1997	22	77	21	72	0.01	10.7	3.8%	1.00 [0.55, 1.82]
Total (95% CI)		**1115**		**1106**			**100.0%**	**0.97 [0.87, 1.09]**
Total events	557		577					

Heterogeneity: Chi² = 4.59, df = 10 (P = 0.92); I² = 0%
Test for overall effect: Z = 0.46 (P = 0.65)

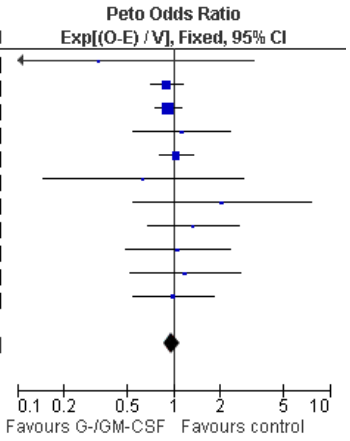


Figure 2. Forest plot of comparison: 6 Sensitivity analysis: Overall survival, outcome: 6.1 GM-CSF versus G-CSF.

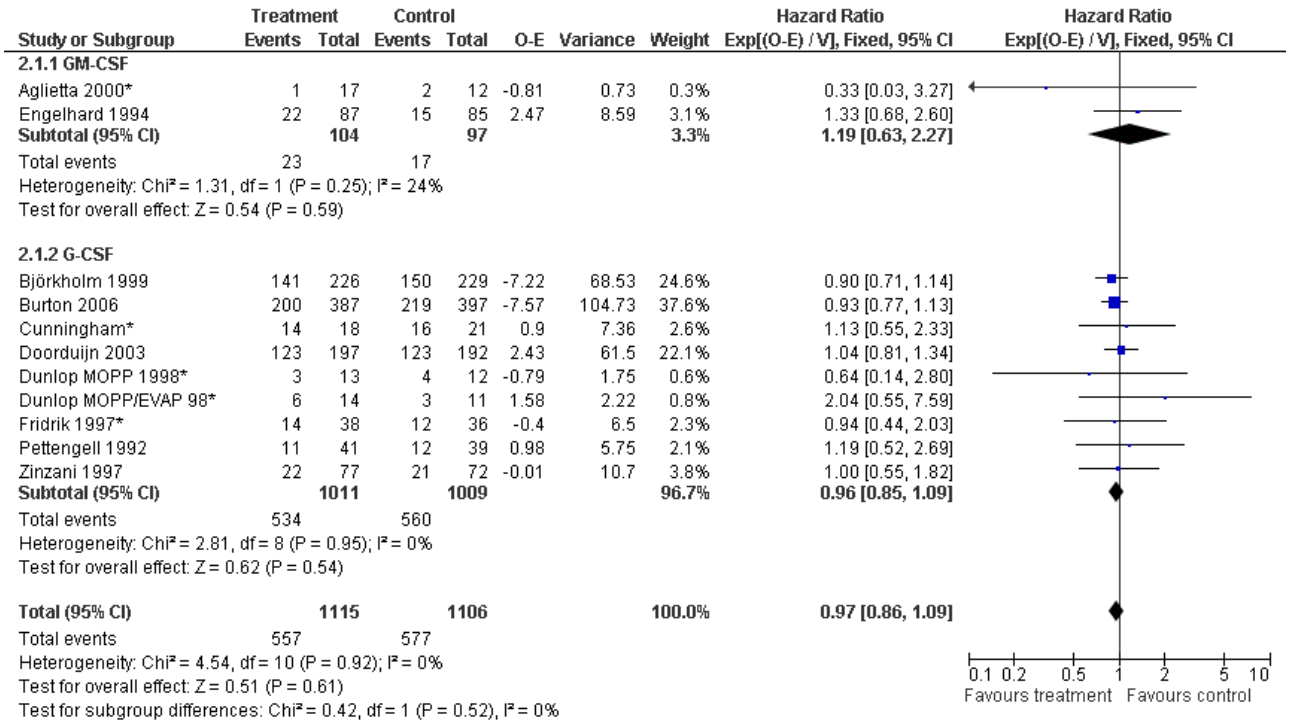


Figure 3. Forest plot of comparison: 6 Sensitivity analysis: Overall survival, outcome: 6.2 HD versus NHL.

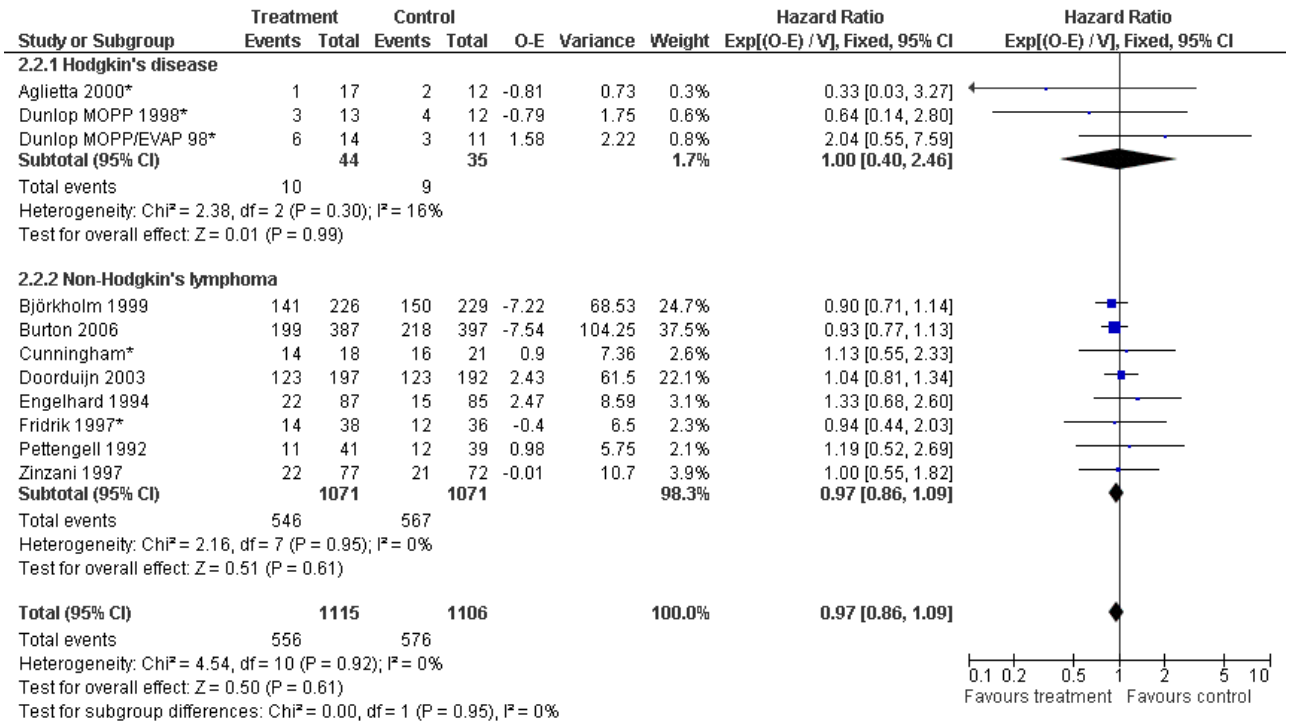


Figure 4. Forest plot of comparison: 6 Sensitivity analysis: Overall survival, outcome: 6.3 Age.

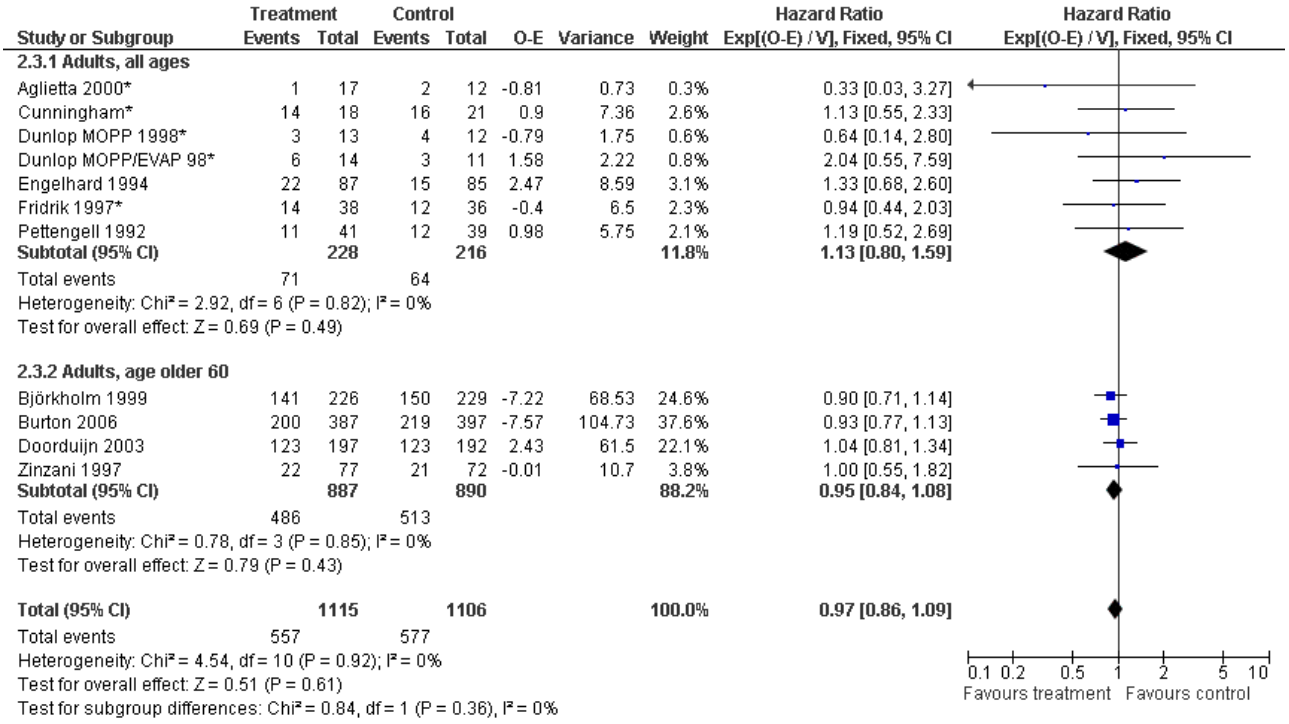


Figure 5. Forest plot of comparison: 6 Sensitivity analysis: Overall survival, outcome: 6.4 Antibiotic prophylaxis.

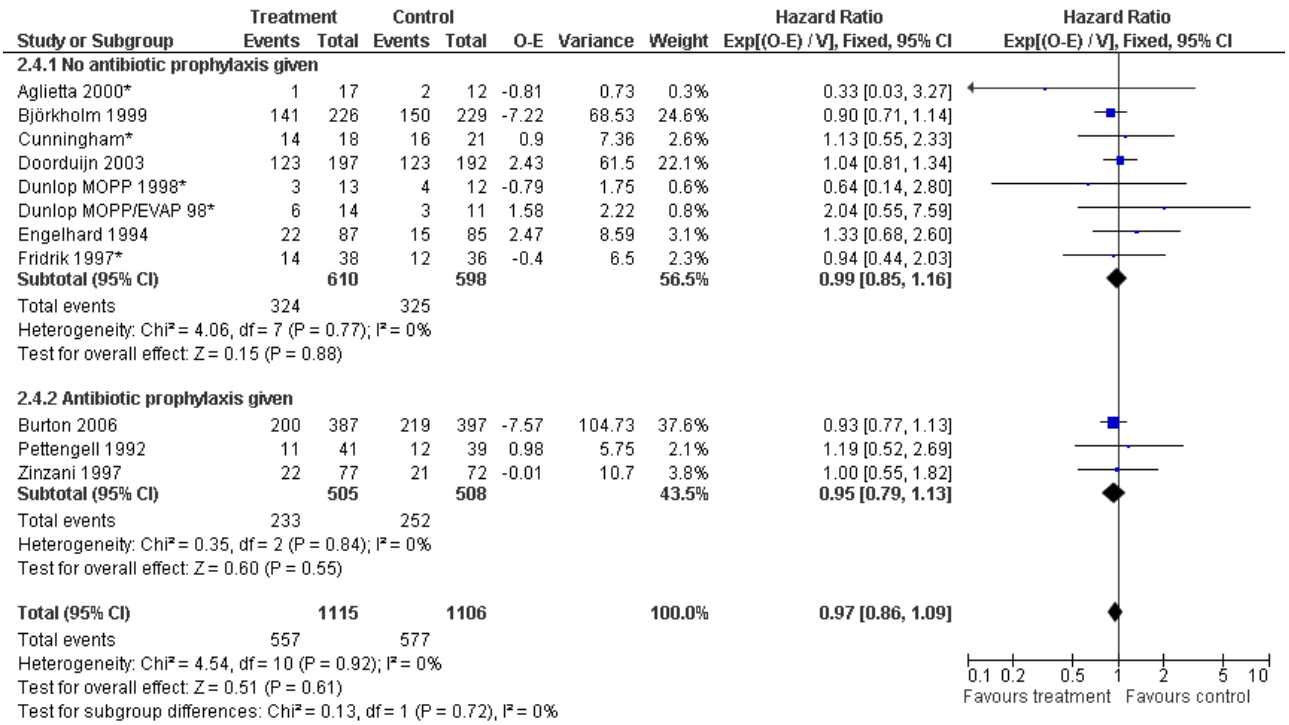


Figure 6. Forest plot of comparison: 6 Sensitivity analysis: Overall survival, outcome: 6.5 Blinded versus open label studies.

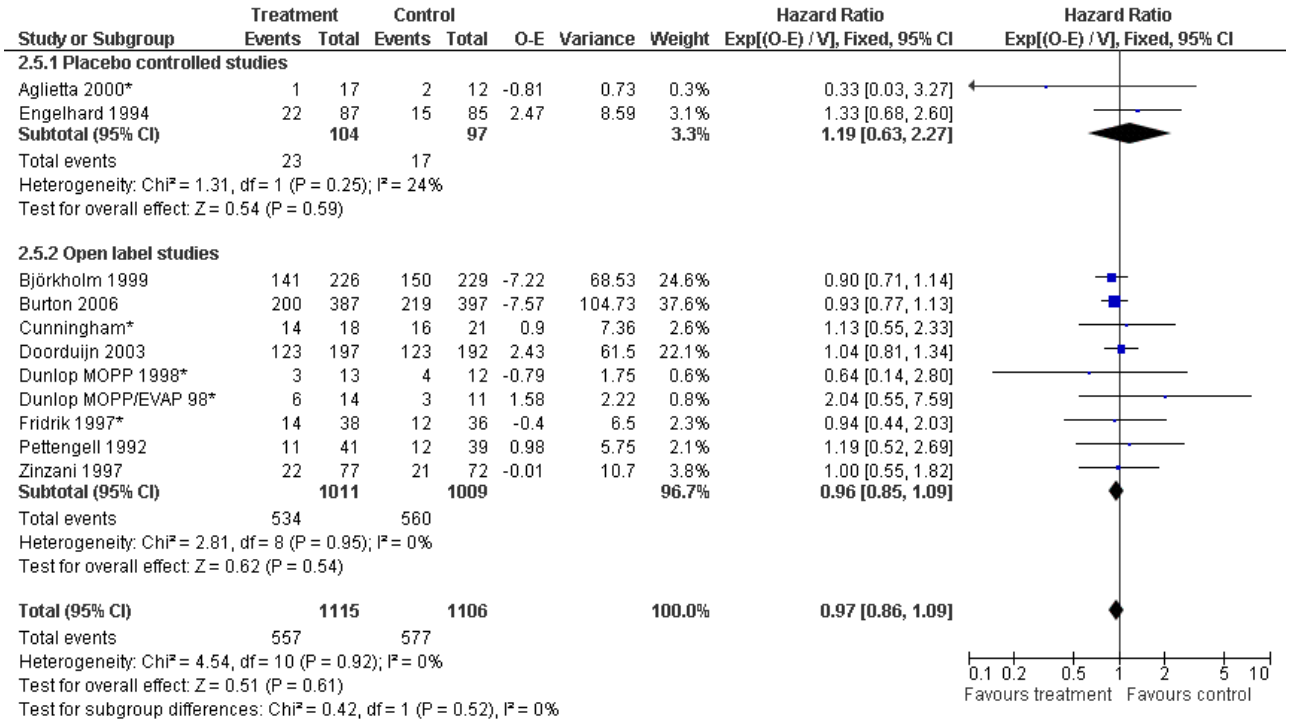


Figure 7. Forest plot of comparison: 6 Sensitivity analysis: Overall survival, outcome: 6.6 Concealed allocation versus concealment of allocation unclear.

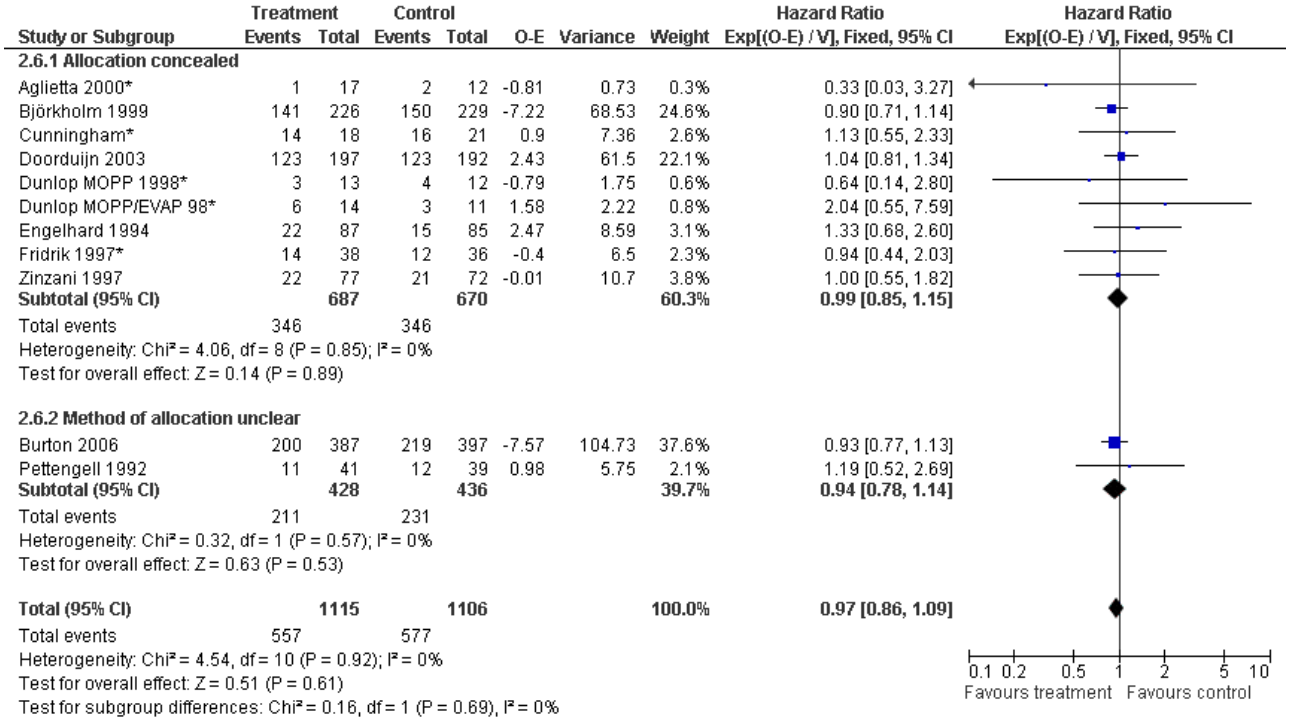


Figure 8. Forest plot of comparison: 6 Sensitivity analysis: Overall survival, outcome: 6.7 Size of studies.

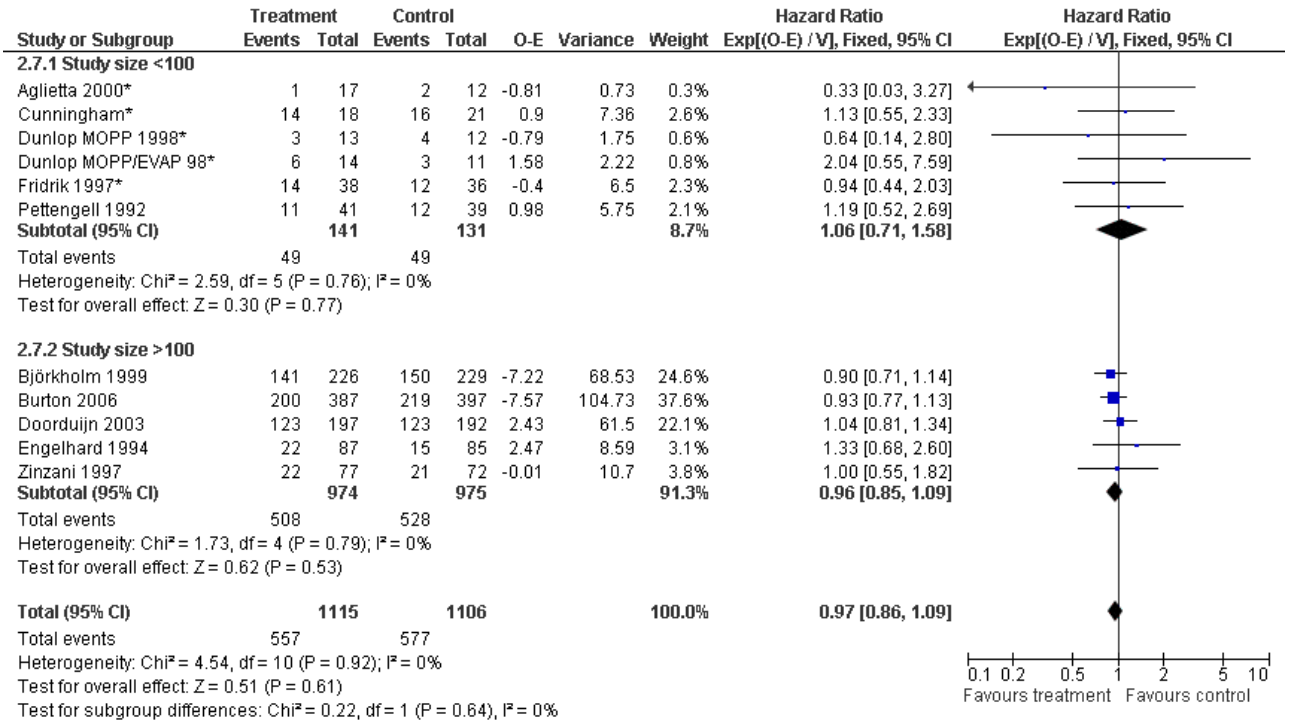
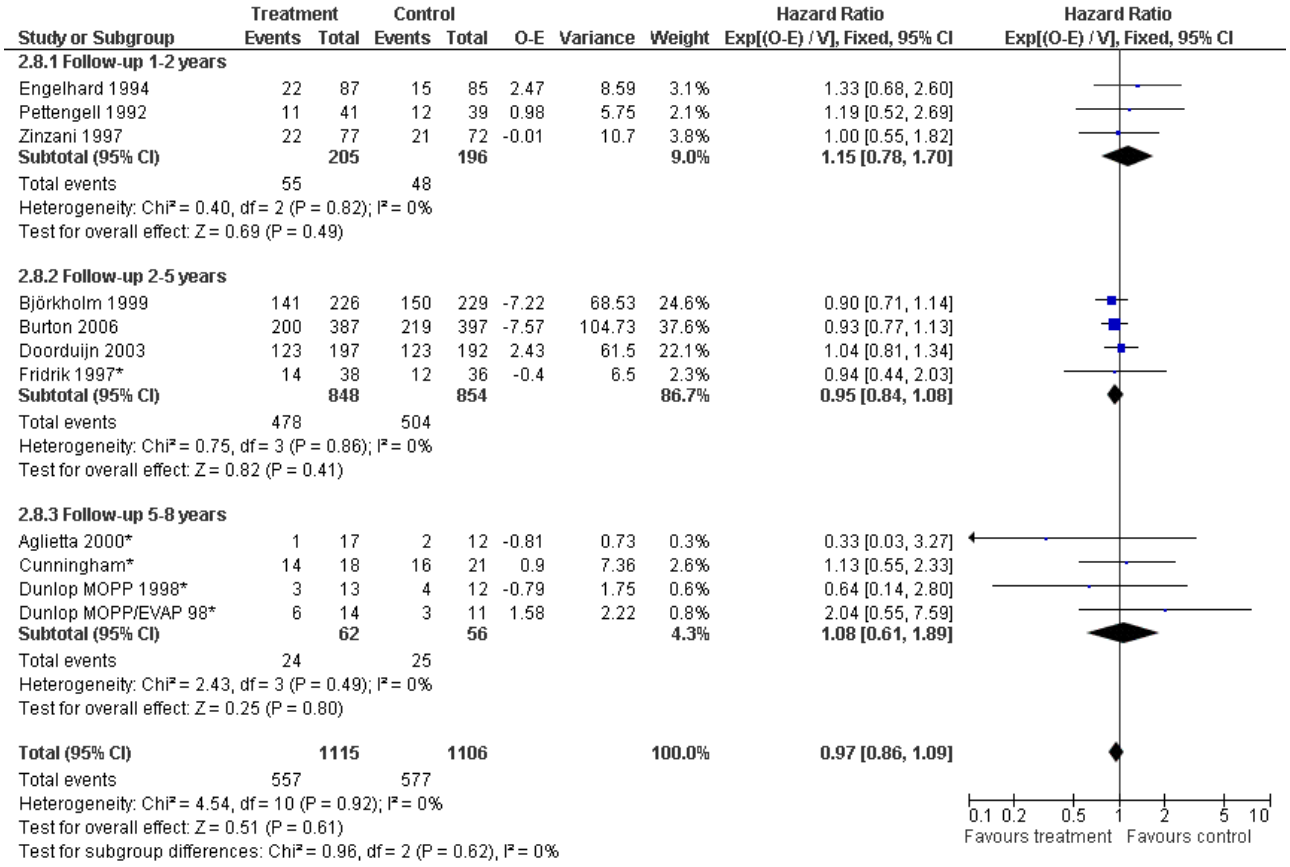


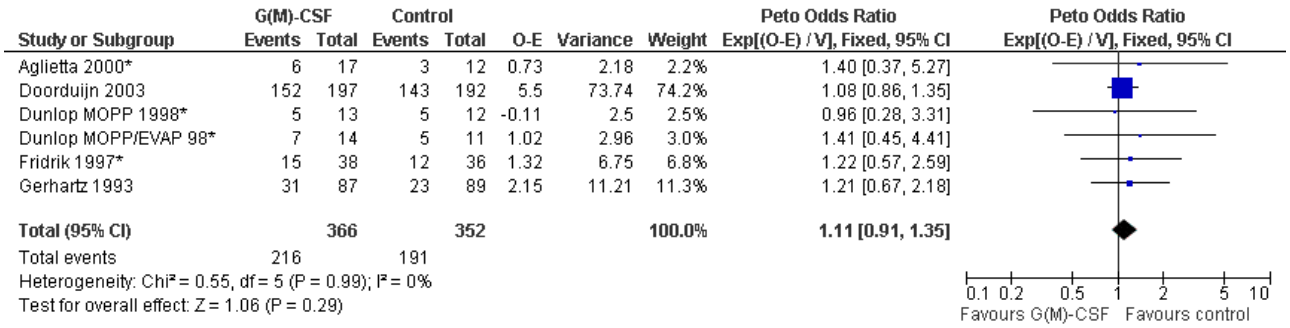
Figure 9. Forest plot of comparison: 6 Sensitivity analysis: Overall survival, outcome: 6.8 Duration of follow-up.



Freedom from treatment failure

FFTF was defined as freedom from progression, relapse of disease or death of any cause. Five studies with 718 patients were included for analysis (Aglietta 2000; Dunlop 1998; Fridrik 1997; Gerhartz 1993; Doorduijn 2003). Again, Dunlop 1998 was analysed by chemotherapy regimen. Aglietta 2000 only provided data for 29 of the 56 patients initially evaluated. When compared to placebo or no treatment, there was no evidence that G-CSF or GM-CSF had a significant effect on FFTF (HR 1.11; 95% CI 0.91 to 1.35) (Figure 10). There was no significant statistical heterogeneity among the trials (chi squared = 0.55, df = 5, P = 0.99). A sensitivity analysis was not performed. Thus, there is no evidence that either G-CSF or GM-CSF improve FFTF rates.

Figure 10. Forest plot of comparison: 1 G-CSF/GM-CSF versus control, outcome: 1.10 Freedom from treatment failure.



Secondary outcome measures

Quality of Life

One study assessed quality of life (QoL) (Doorduijn 2003) with the following questionnaires: the EuroQol questionnaire, the EORTC Quality of Life Questionnaire and the Multidimensional Fatigue Inventory. Of the 389 patients initially included in the trial, 162 patients were asked to participate in the QoL study; 19% refused. Of the participating patients, 96% returned their questionnaires

during the study period and 88% in the follow-up period. Overall, no differences in QoL between the G-CSF and the control group were detected.

Neutropenia

Seven studies with 1013 patients were included in this analysis (Cunningham*; Pettengell 1992; Fridrik 1997*; Gisselbrecht 1997; Zinzani 1997; Aglietta 2000*; Ösby 2003). Ösby 2003 was analysed by chemotherapy regimen (Ösby CHOP 2003 , Ösby CNOP 2003). The risk of suffering from neutropenia, defined as absolute neutrophil count (ANC) below 0.5 x 10^9/litre, was reduced by 33% for patients treated with G-CSF or GM-CSF (RR 0.67; 95% CI 0.60 to 0.73) (Figure 11). There was significant statistical heterogeneity among the trials (chi squared = 14.98, df = 7, P = 0.04), indicating that the variation in the effect of G-CSF and GM-CSF was larger than would be expected to result from chance alone. Sensitivity analyses (see comparison 3) revealed significant between group heterogeneity for prophylactic administration of antibiotic treatment during chemotherapy (P = 0.0022). A stronger treatment effect was observed in trials with antibiotic prophylaxis (RR 0.43; 95% CI 0.31 to 0.60, 2 trials with N = 229) compared to trials without antibiotic prophylaxis (RR 0.72; 95% CI 0.65 to 0.79, 5 trials with N =784), P value for difference between subgroups: 0.0042); see Figure 12. Other sensitivity analyses showed no significant differences with respect to G-CSF versus GM-CSF, HD versus NHL, age, haemato-toxicity, blinded versus open label, concealment of allocation, quality and size of study and publication type (Figure 13; Figure 14; Figure 15; Figure 16; Figure 17; Figure 18; Figure 19; Figure 20; Figure 21). There was no indication of bias in the meta-analysis.

Figure 11. Forest plot of comparison: 1 G-CSF/GM-CSF versus control, outcome: 1.1 Neutropenia.

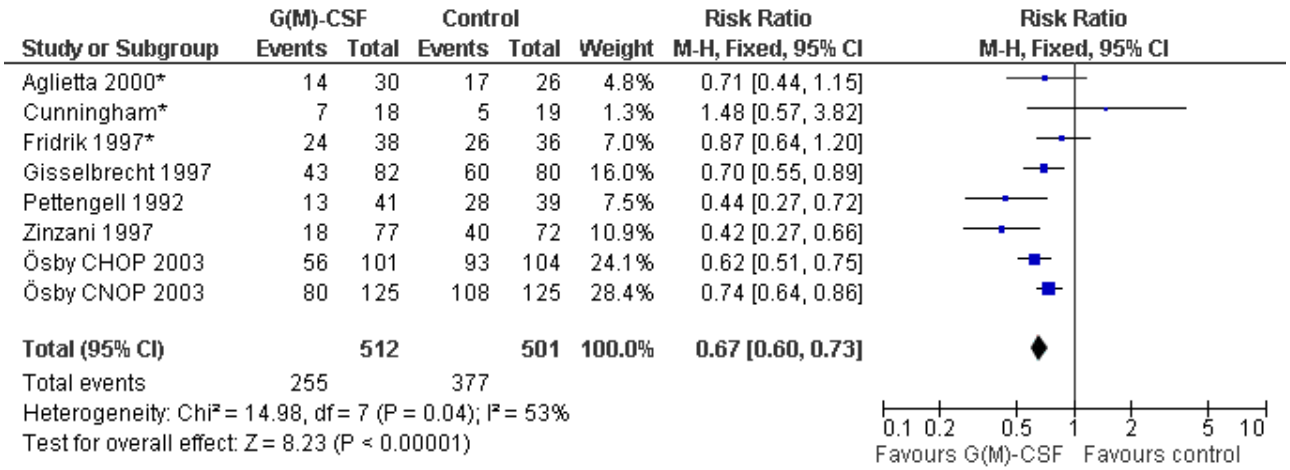


Figure 12. Forest plot of comparison: 2 Sensitivity analysis: Neutropenia, outcome: 2.5 Use of antibiotic prophylaxis.

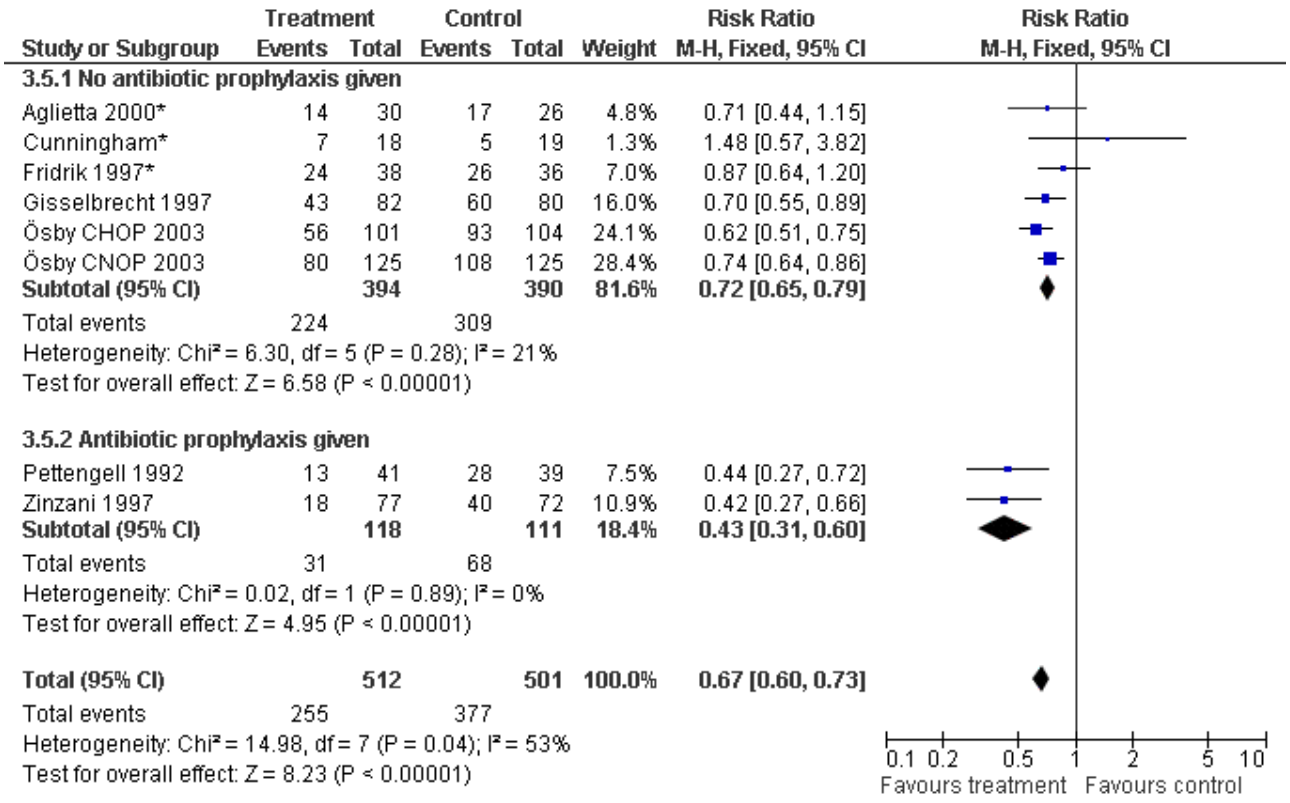


Figure 13. Forest plot of comparison: 2 Sensitivity analysis: Neutropenia, outcome: 2.1 G-CSF versus GM-CSF.

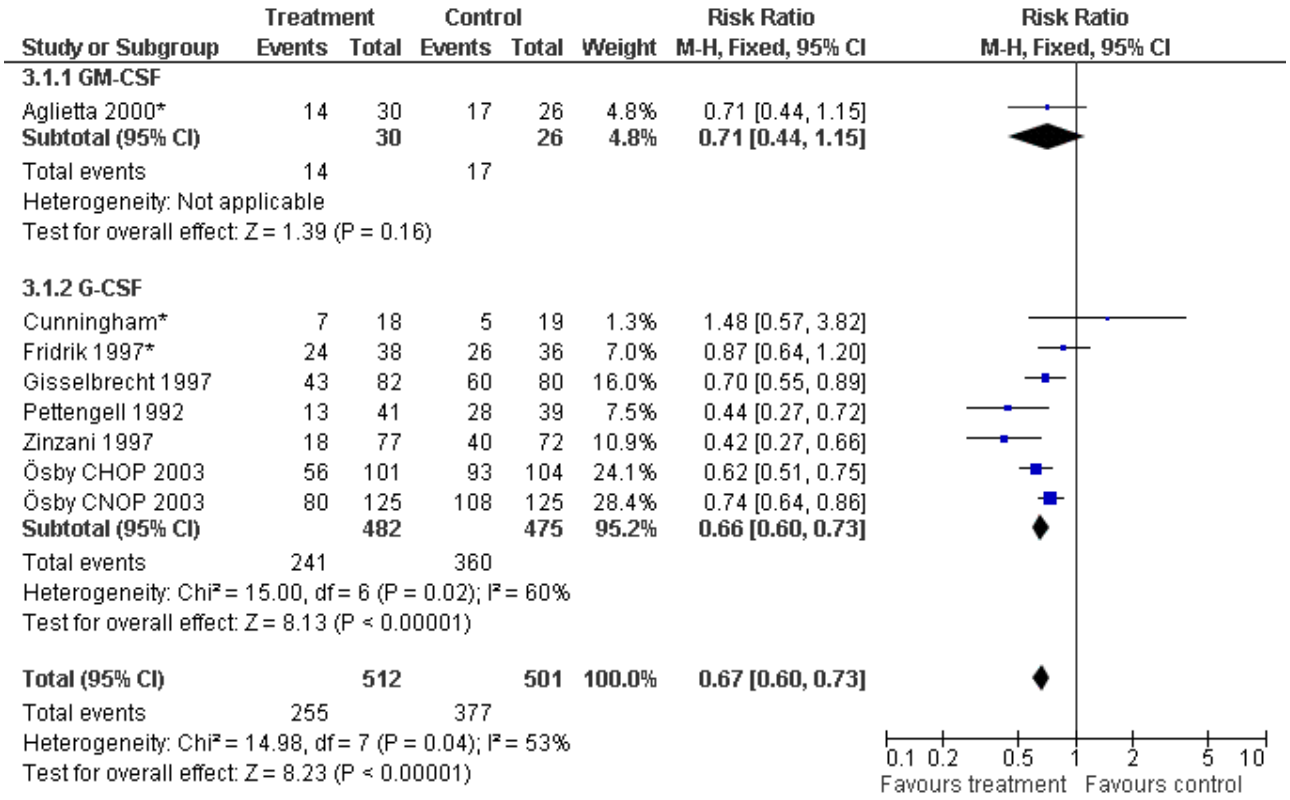


Figure 14. Forest plot of comparison: 2 Sensitivity analysis: Neutropenia, outcome: 2.2 HD versus NHL.

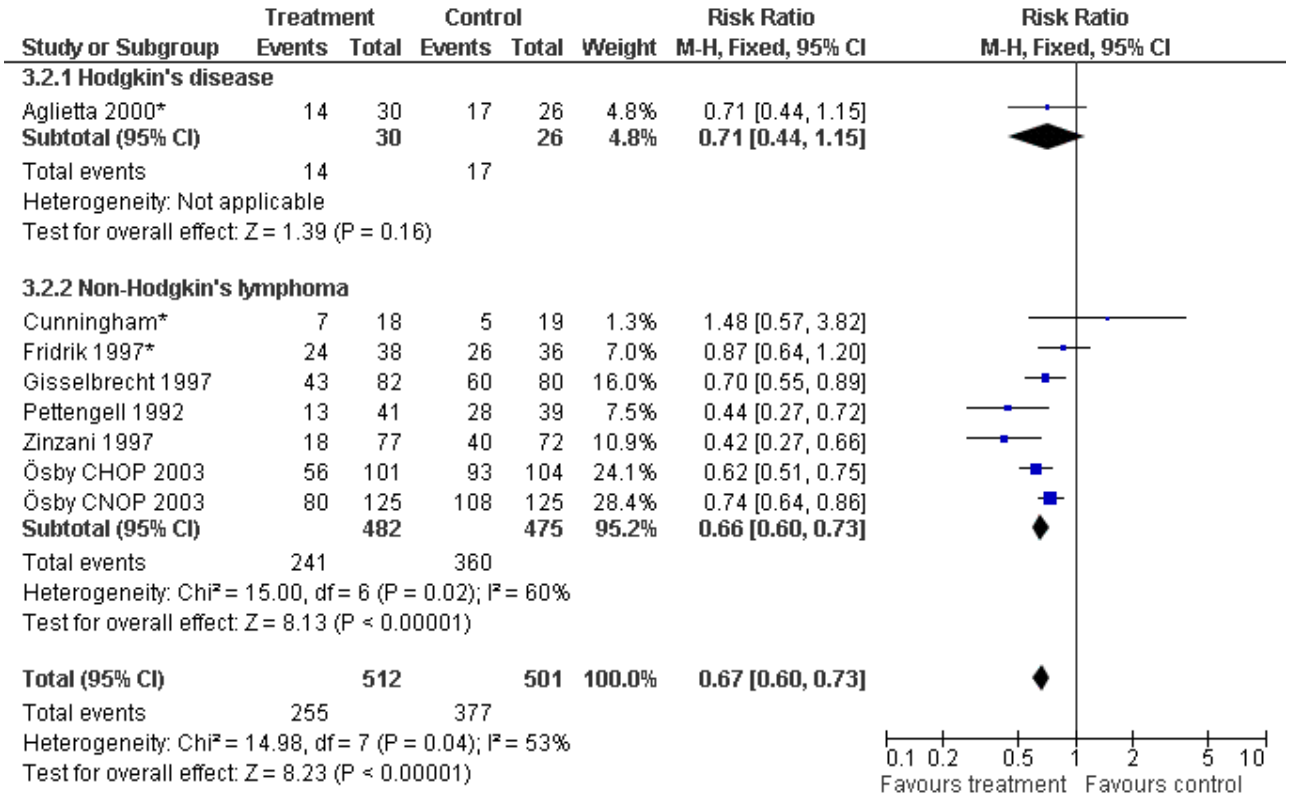


Figure 15. Forest plot of comparison: 2 Sensitivity analysis: Neutropenia, outcome: 2.3 Age.

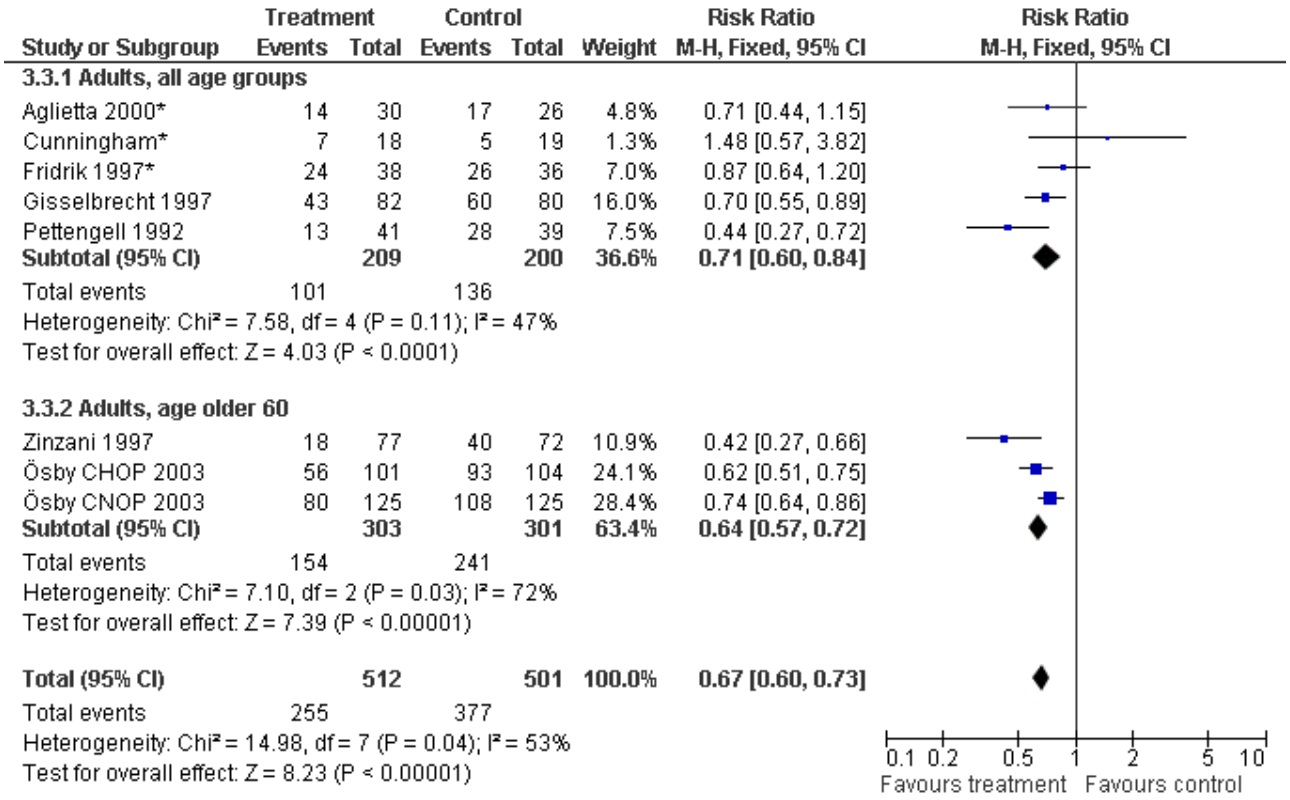


Figure 16. Forest plot of comparison: 2 Sensitivity analysis: Neutropenia, outcome: 2.4 Haematotoxicity.

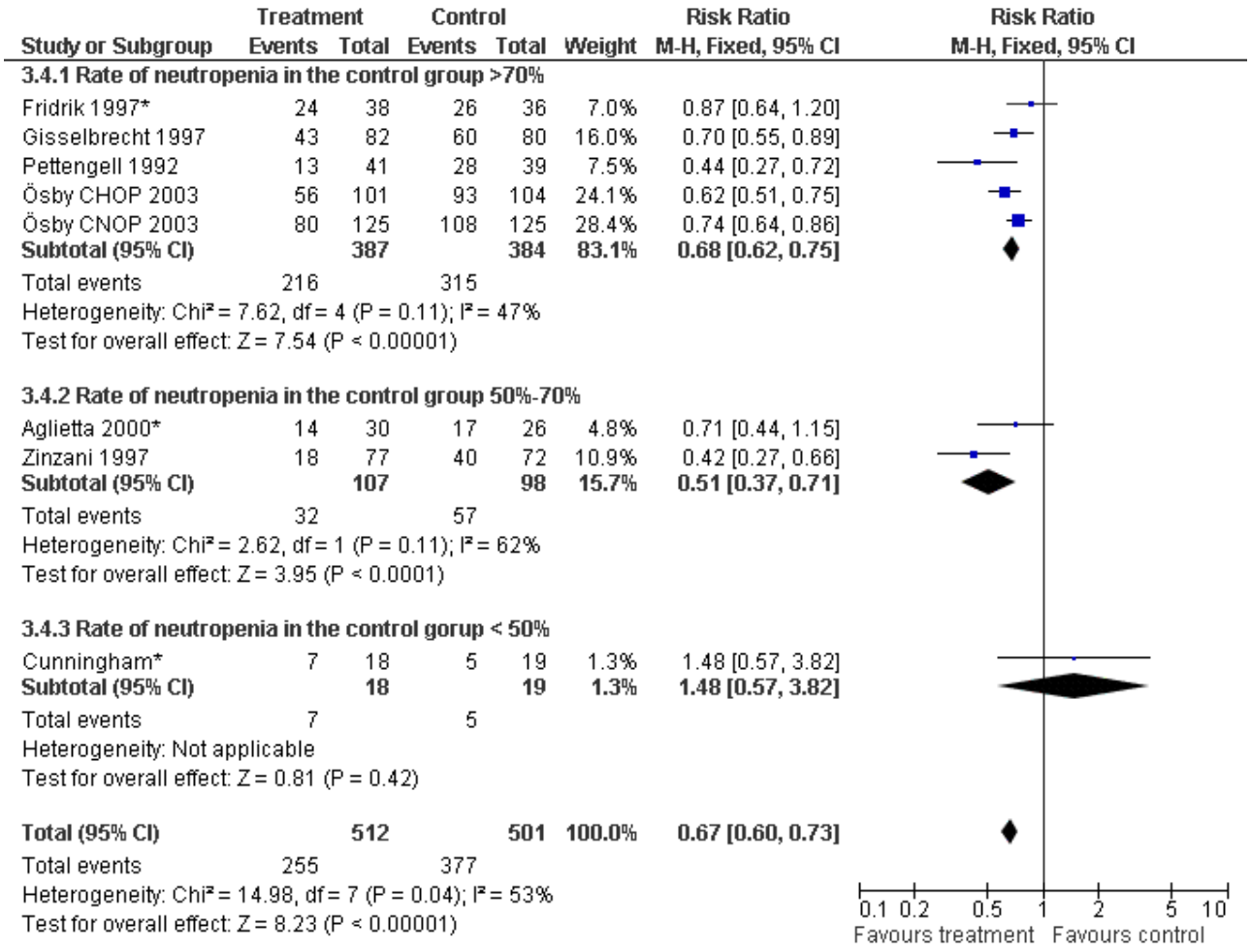


Figure 17. Forest plot of comparison: 2 Sensitivity analysis: Neutropenia, outcome: 2.6 Blinded versus openlabel studies.

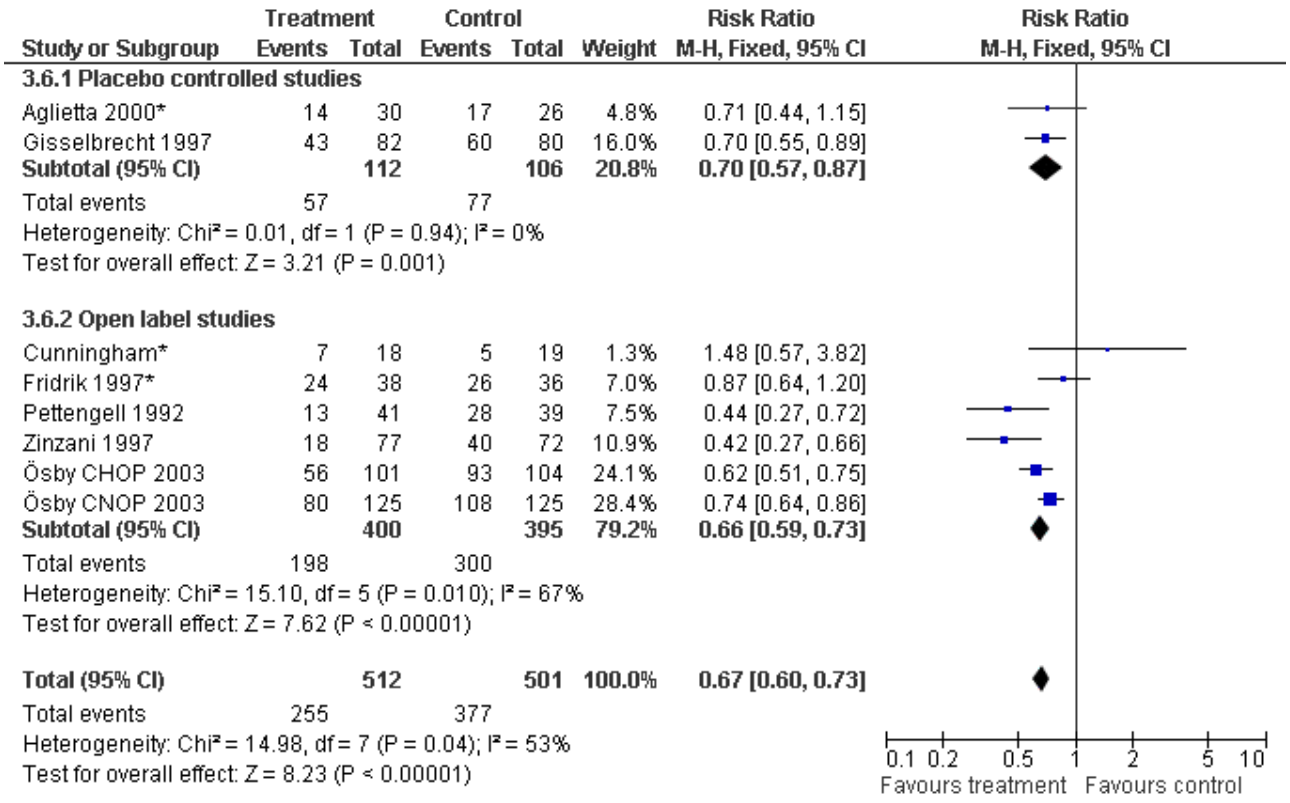


Figure 18. Forest plot of comparison: 2 Sensitivity analysis: Neutropenia, outcome: 2.7 Concealed versus unclear method of allocation.

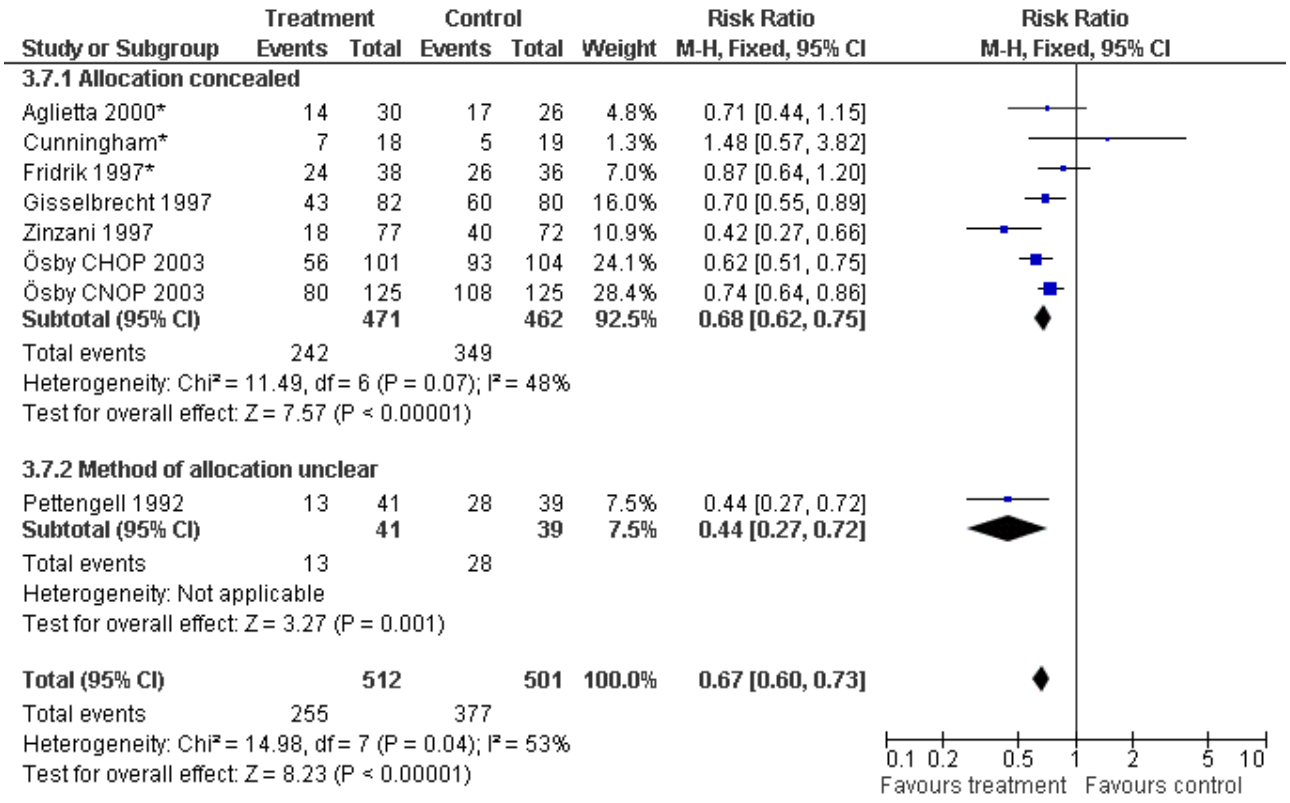


Figure 19. Forest plot of comparison: 2 Sensitivity analysis: Neutropenia, outcome: 2.8 Published and reported data versus unpublished or unreported data.

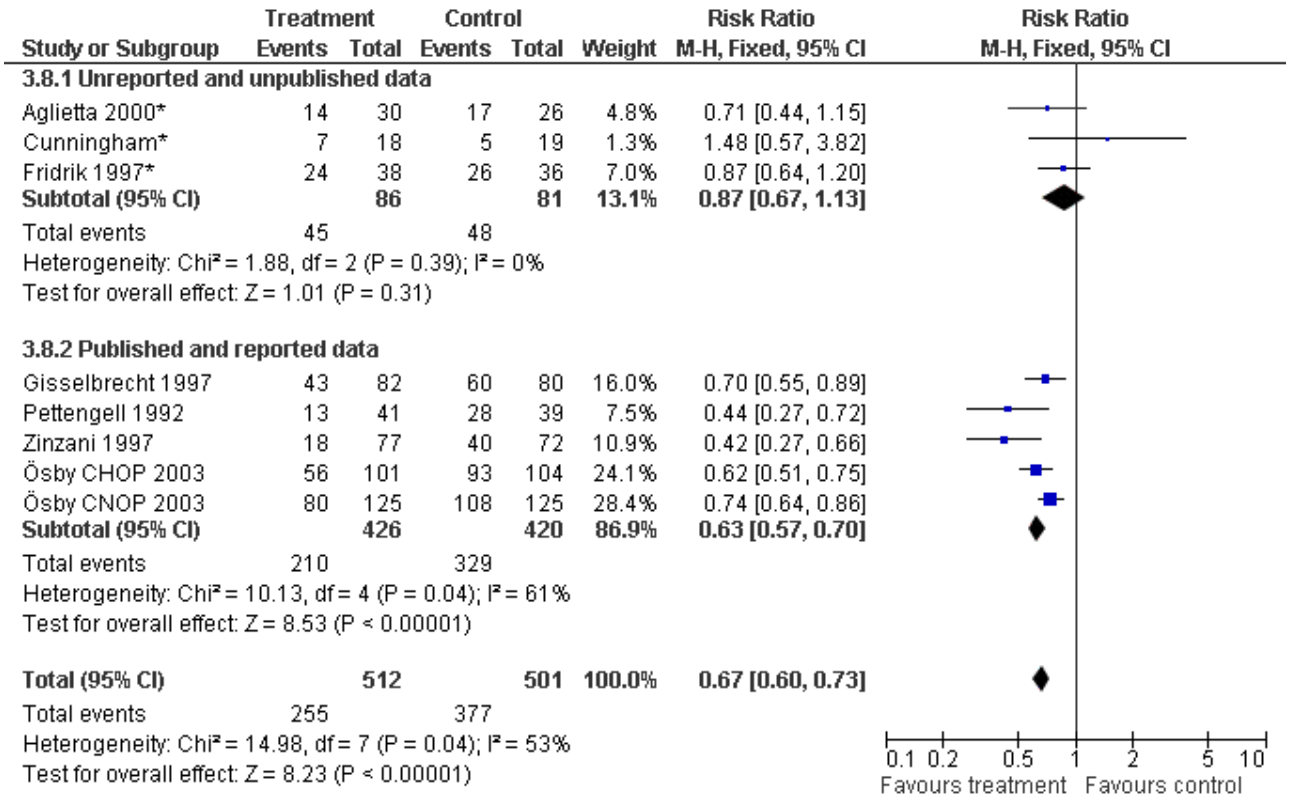


Figure 20. Forest plot of comparison: 2 Sensitivity analysis: Neutropenia, outcome: 2.9 Size of study.

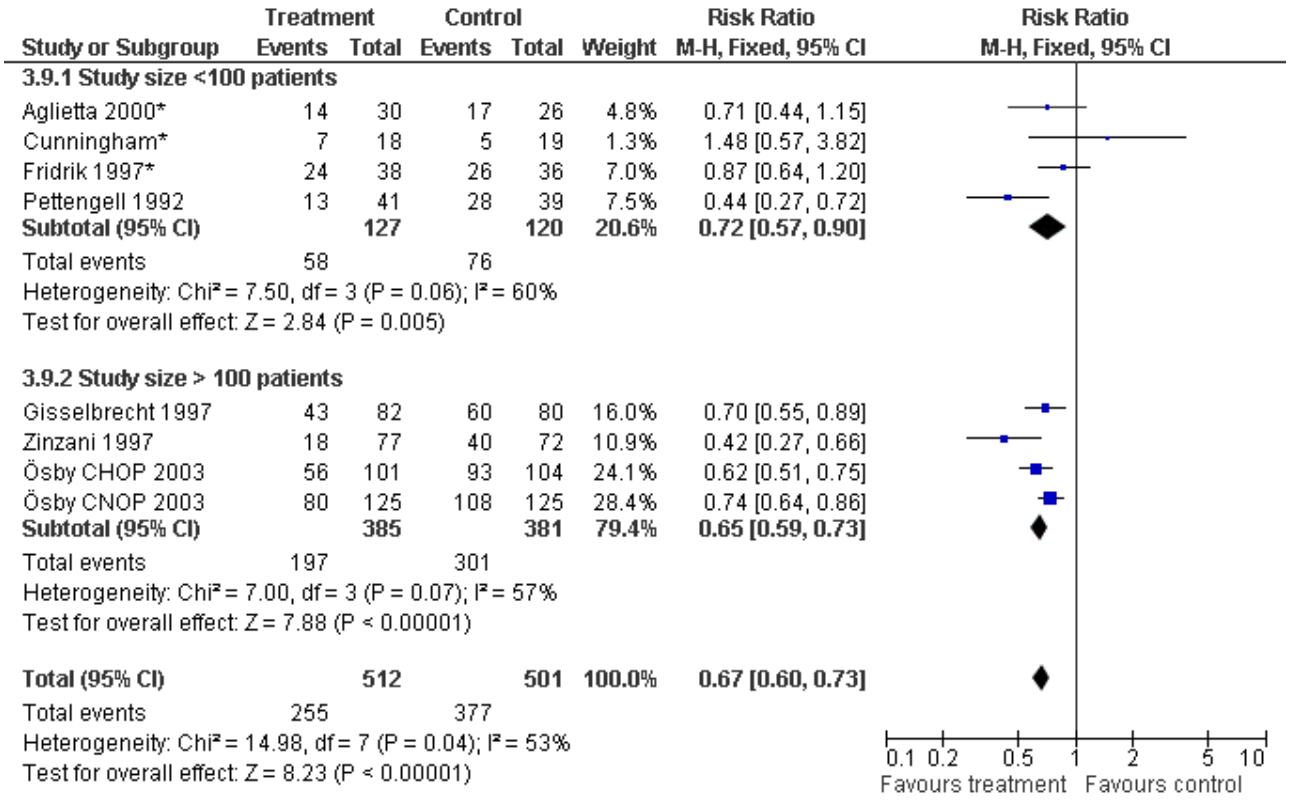
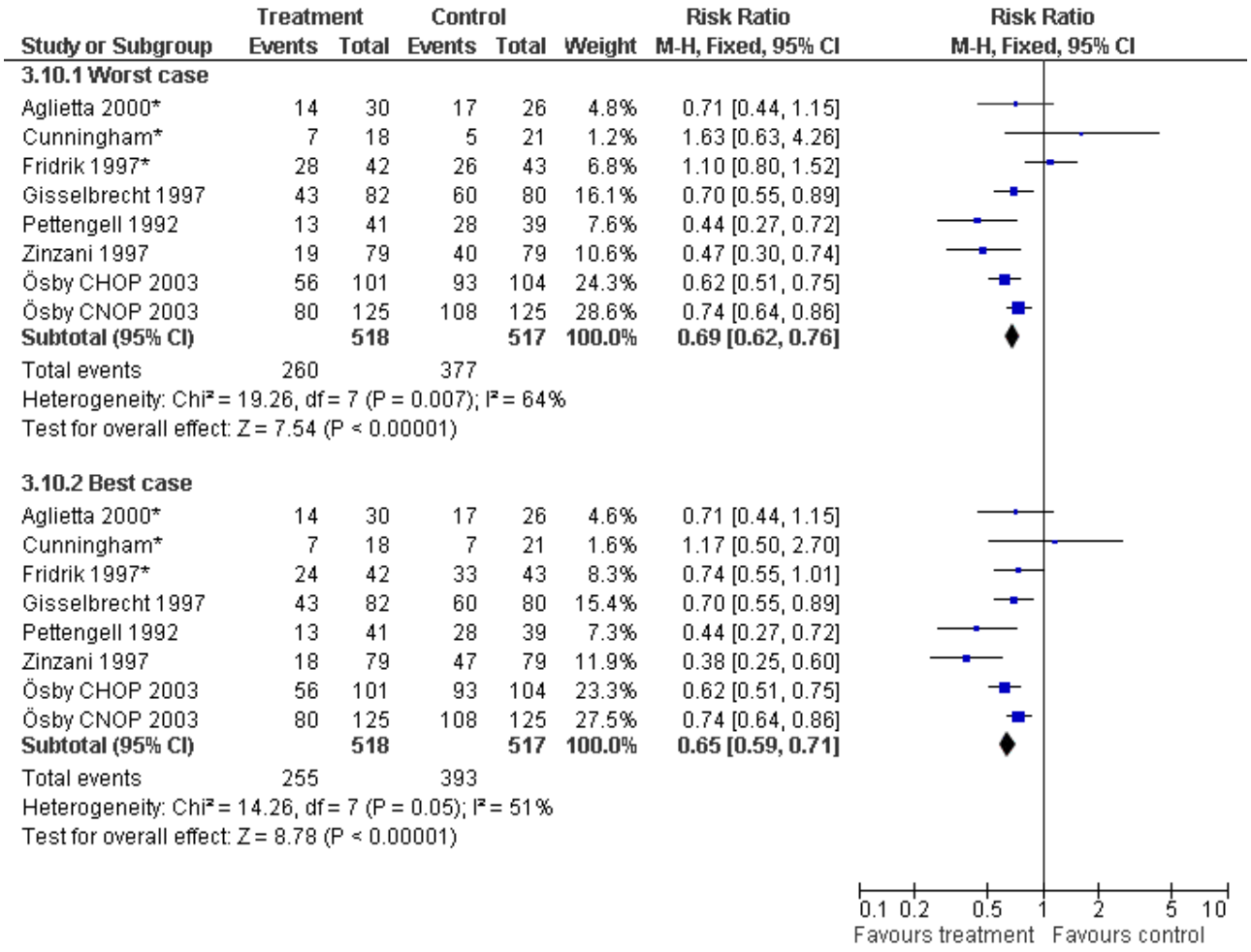


Figure 21. Forest plot of comparison: 2 Sensitivity analysis: Neutropenia, outcome: 2.10 Worst case-best case.



Febrile neutropenia, ANC < 1.0 x 10^9/litre and febrile temperatures

Four studies including 360 patients were analysed (Pettengell 1992; Fridrik 1997; Gisselbrecht 1997; Dunlop 1998). Dunlop 1998 was analysed by chemotherapy regimen (Dunlop MOPP 1998 ; Dunlop MOPP/EVAP 98). The risk of febrile neutropenia, defined as ANC below 1.0 x 10^9/litre and febrile temperatures, was reduced by 26% (RR 0.74; 95% CI 0.62 to 0.89); see Figure 22. There was no obvious statistical heterogeneity among the trials (chi squared = 4.31, df = 4, P = 0.37). All included studies evaluated G-CSF and had an underlying risk to develop febrile neutropenia of at least 36% in the control group. Data for GM-CSF were not available. Sensitivity analyses (tumour entity, antibiotic prophylaxis, quality and size of study; comparison 4) did not show significant differences (Figure 23; Figure 24; Figure 25; Figure 26; Figure 27; Figure 28). These data suggest that G-CSF significantly reduces the risk for febrile neutropenia.

Figure 22. Forest plot of comparison: 1 G-CSF/GM-CSF versus control, outcome: 1.2 Febrile Neutropenia, ANC < 1000.

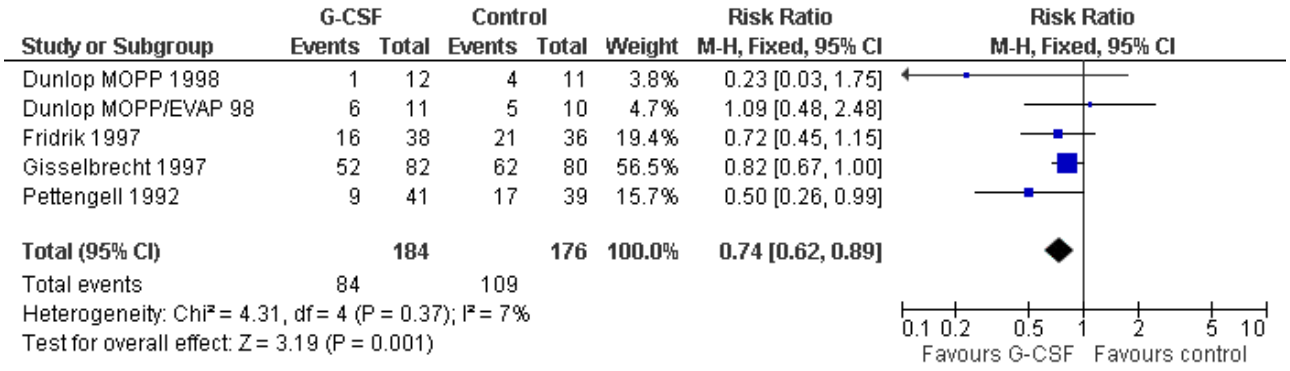


Figure 23. Forest plot of comparison: 3 Sensitivity analysis: Febrile Neutropenia, outcome: 3.1 HD versus NHL.

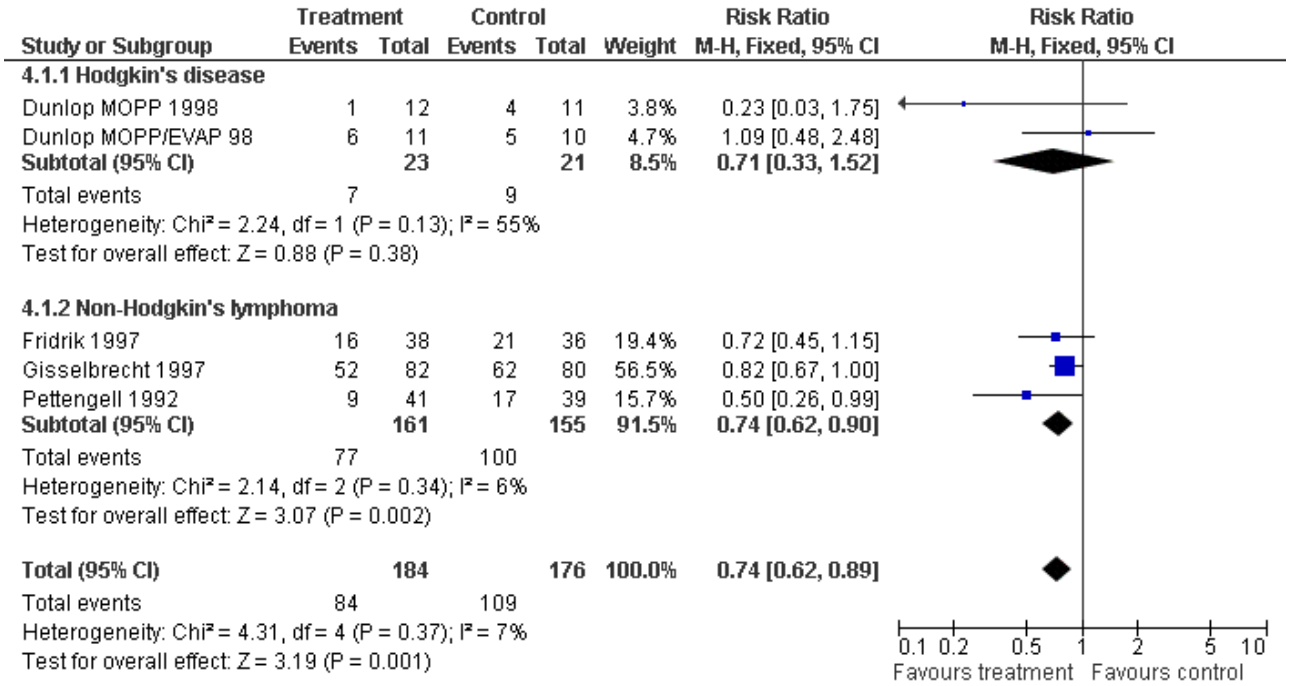


Figure 24. Forest plot of comparison: 3 Sensitivity analysis: Febrile Neutropenia, outcome: 3.2 Use of antibiotic prophylaxis.

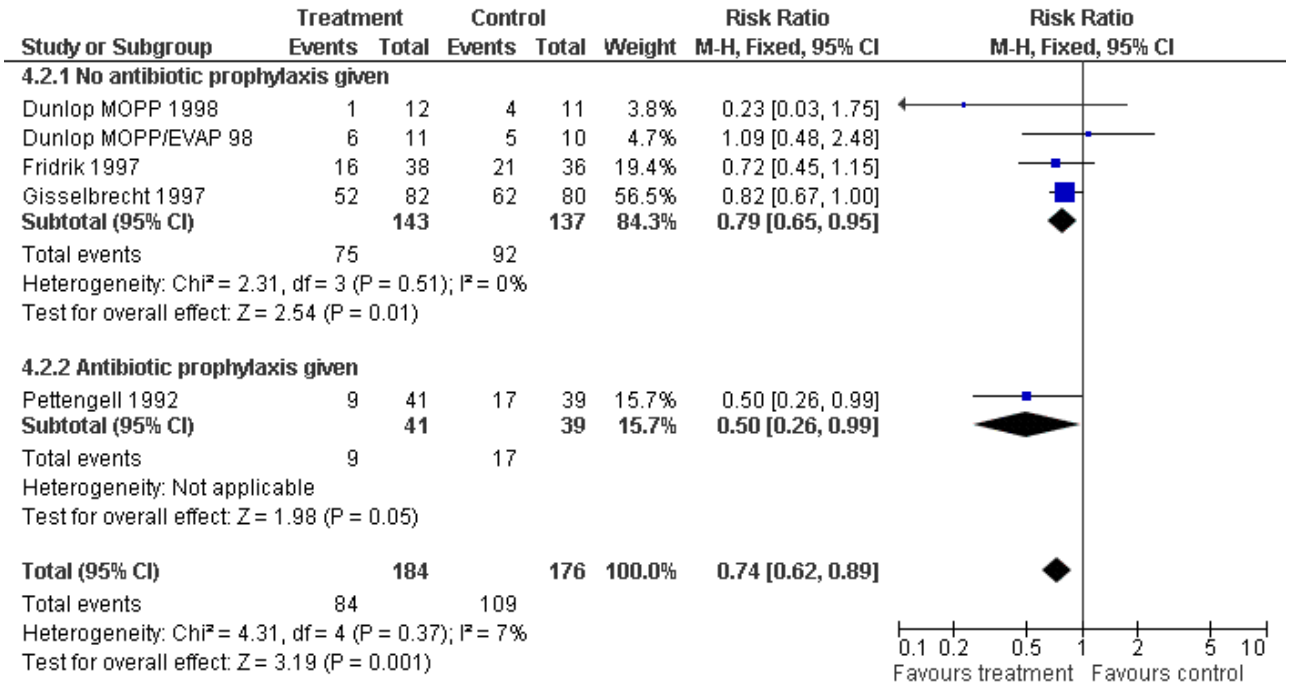


Figure 25. Forest plot of comparison: 3 Sensitivity analysis: Febrile Neutropenia, outcome: 3.3 Blinded versus open label studies.

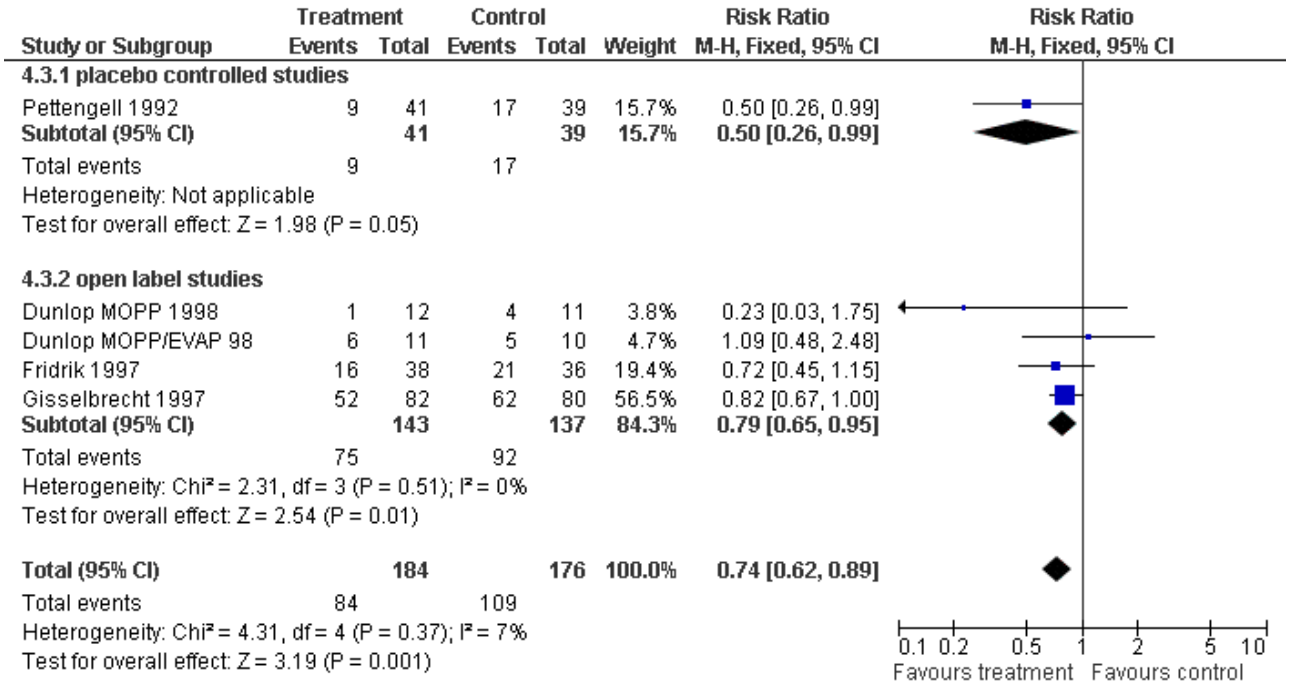


Figure 26. Forest plot of comparison: 3 Sensitivity analysis: Febrile Neutropenia, outcome: 3.4 Concealed versus unclear method of allocation.

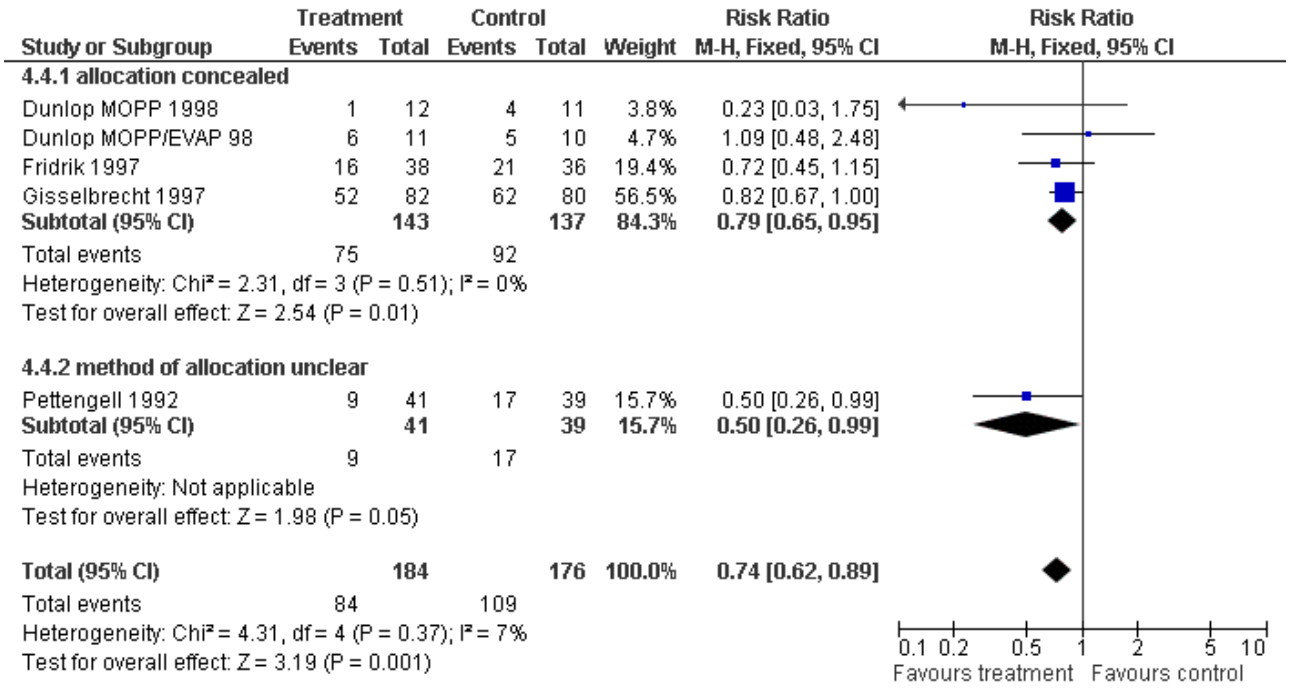


Figure 27. Forest plot of comparison: 3 Sensitivity analysis: Febrile Neutropenia, outcome: 3.5 Size of study.

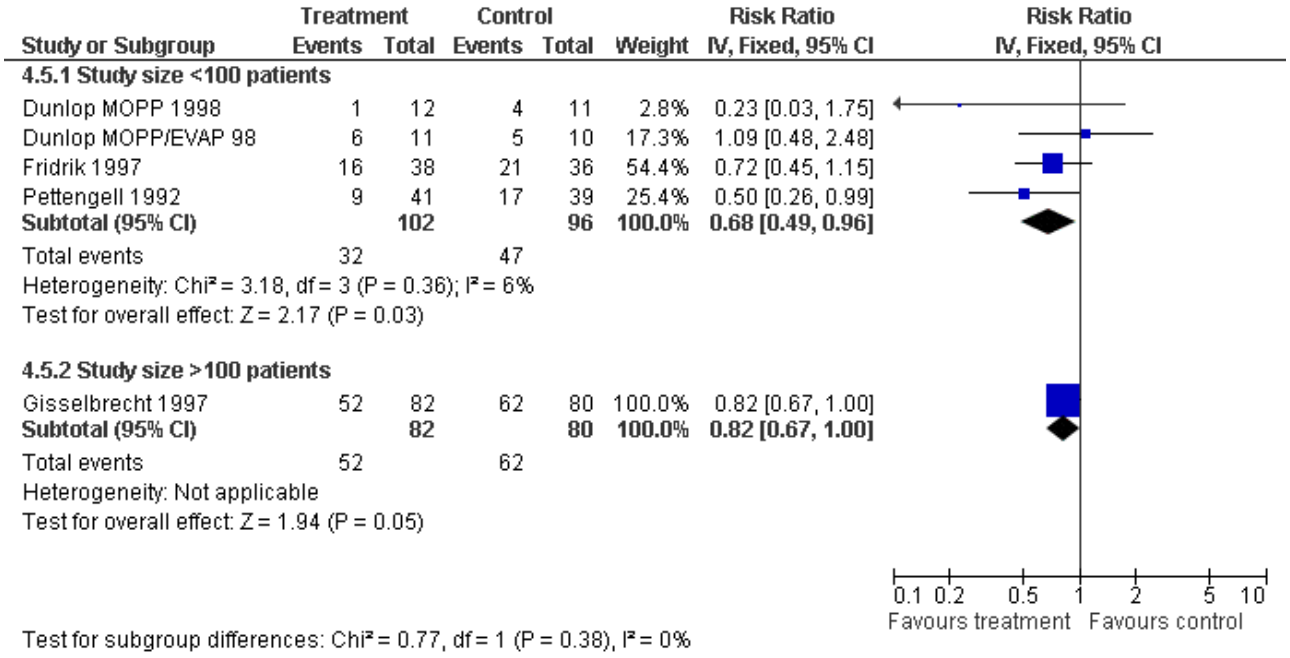
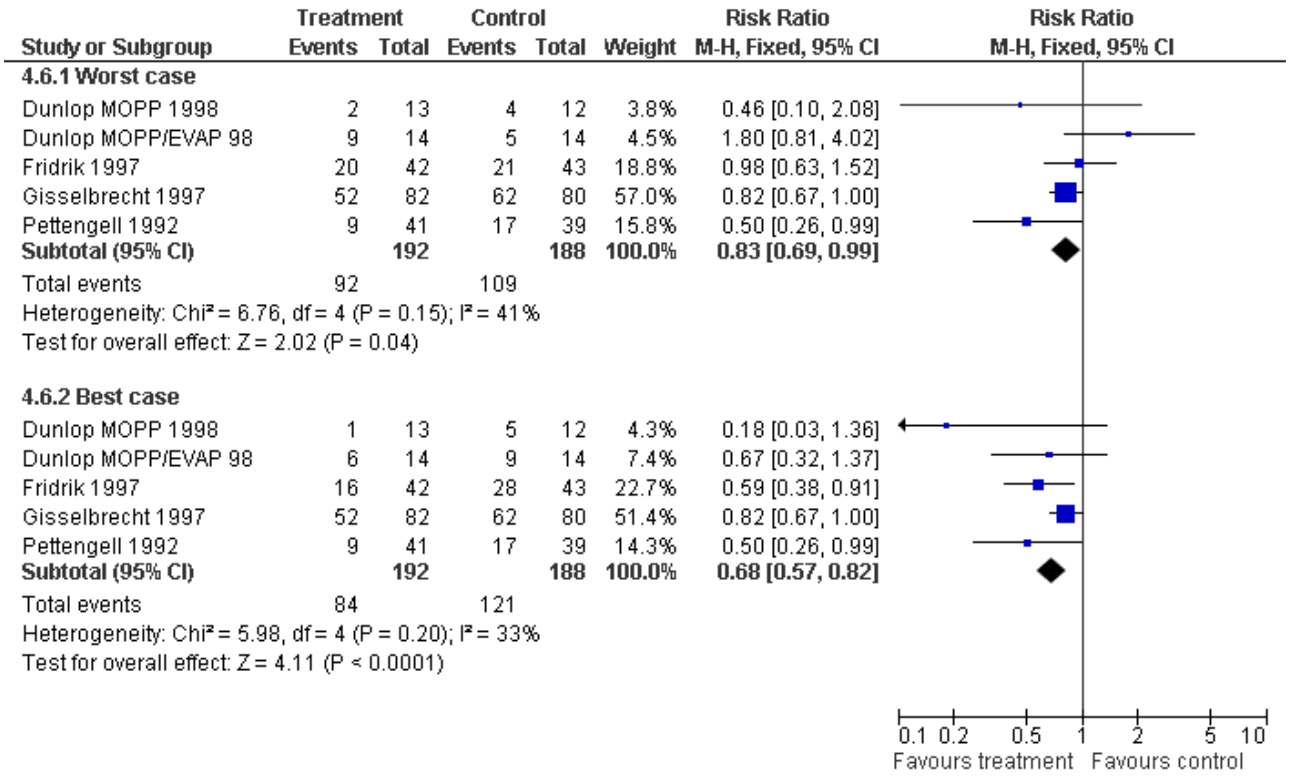


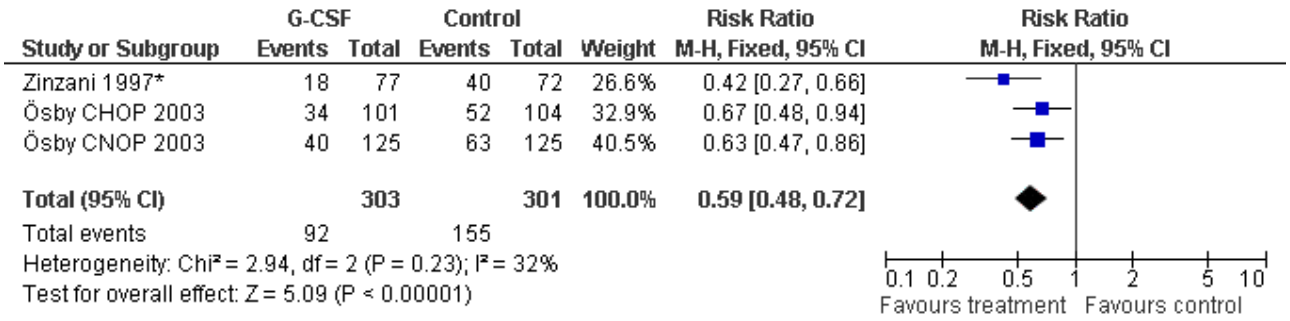
Figure 28. Forest plot of comparison: 3 Sensitivity analysis: Febrile Neutropenia, outcome: 3.6 Worst case-best case.



Febrile neutropenia, ANC < 0.5 x 10^9/litre and febrile temperatures

Two studies, one with two chemotherapy regimens, including 604 patients were analysed. Febrile neutropenia was defined as ANC below 0.5 x 10^9/litre and febrile temperatures (Zinzani 1997*; Ösby 2003). The risk for febrile neutropenia was reduced by 41% (RR 0.59; 95% CI 0.48 to 0.72); see Figure 29. There was no statistical heterogeneity among the trials (chi squared = 2.94, df = 2, P = 0.23). All included studies evaluated G-CSF and had an underlying risk to develop febrile neutropenia of at least 50% in the control group. Data for GM-CSF were not available. A sensitivity analysis was not done. These data suggest that G-CSF significantly reduces the risk for febrile neutropenia.

Figure 29. Forest plot of comparison: 1 G-CSF/GM-CSF versus control, outcome: 1.3 Febrile Neutropenia, ANC < 500.



Infection

Nine studies, two with two different chemotherapy regimens, with 1292 patients reporting microbiologically or clinically documented infection were included in the analysis (Pettengell 1992; Bastion 1993; Gerhartz 1993; Souêtre 1994; Fridrik 1997; Zinzani 1997; Dunlop 1998; Björkholm 1999; Aglietta 2000*). When infections were documented by both microbiological and clinical methods, only the microbiologically documented infections were included as these are less prone to bias (Souêtre 1994; Gisselbrecht 1997). The risk of developing an infection was reduced by 26% (RR 0.74; 95% CI 0.64 to 0.85); see Figure 30. Inclusion of either microbiological or clinical data did change the result (data not shown). There was no significant statistical heterogeneity among the trials (chi squared = 12.02, df = 10, P = 0.28). Sensitivity analyses (tumour entity, antibiotic prophylaxis, quality and size of study; comparison 5) did not show significant differences (Figure 31; Figure 32; Figure 33;

Figure 34; Figure 35; Figure 36; Figure 37; Figure 38; Figure 39). These data suggest that G-CSF and GM-CSF significantly reduce the risk of infection.

Figure 30. Forest plot of comparison: 1 G-CSF/GM-CSF versus control, outcome: 1.4 Infection.

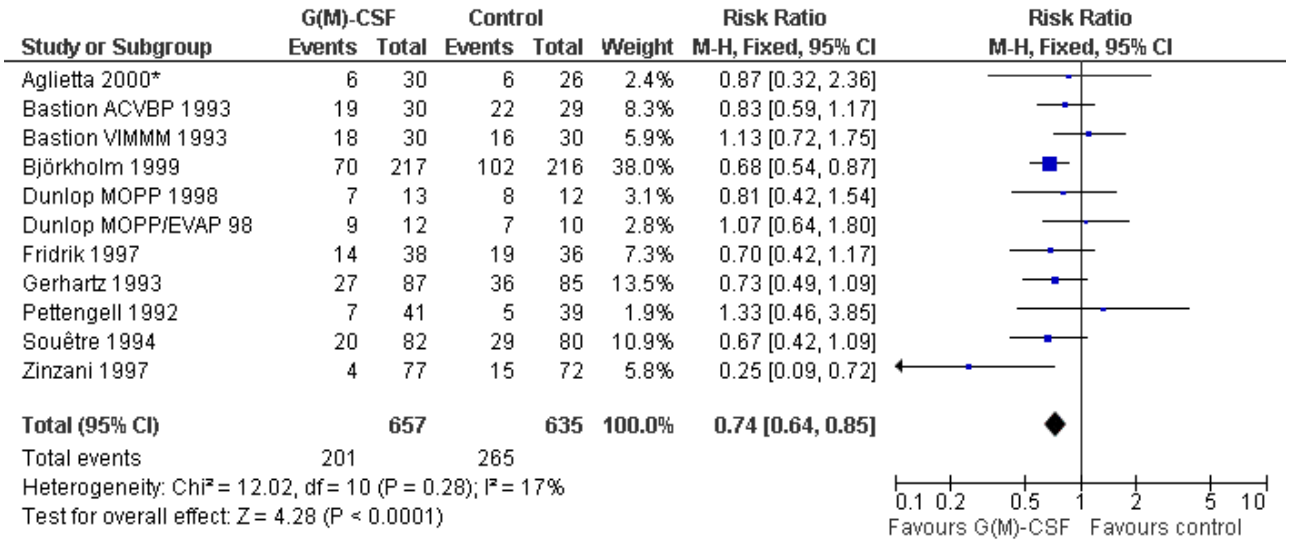


Figure 31. Forest plot of comparison: 4 Sensitivity analysis: Infection, outcome: 4.1 G-CSF versus GM-CSF.

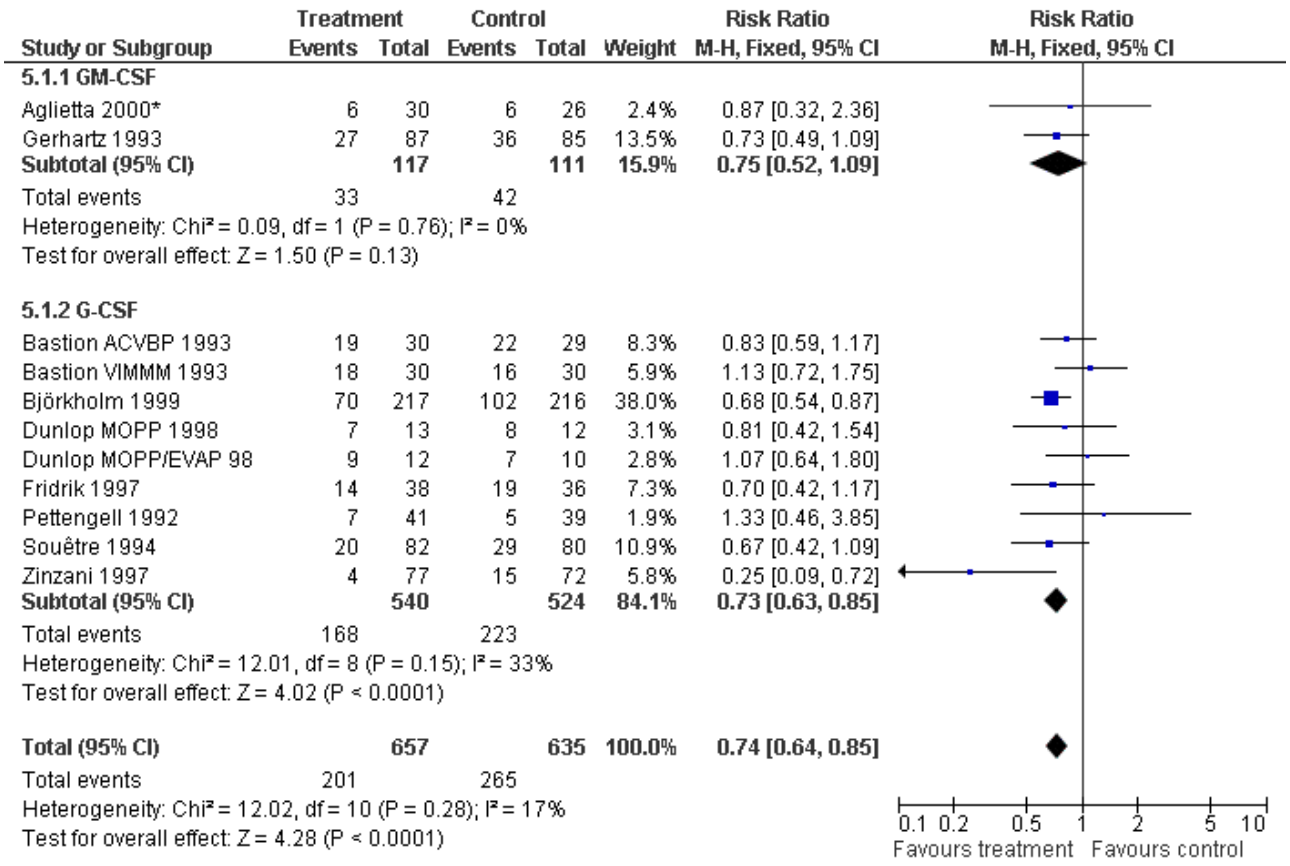


Figure 32. Forest plot of comparison: 4 Sensitivity analysis: Infection, outcome: 4.2 HD versus NHL.

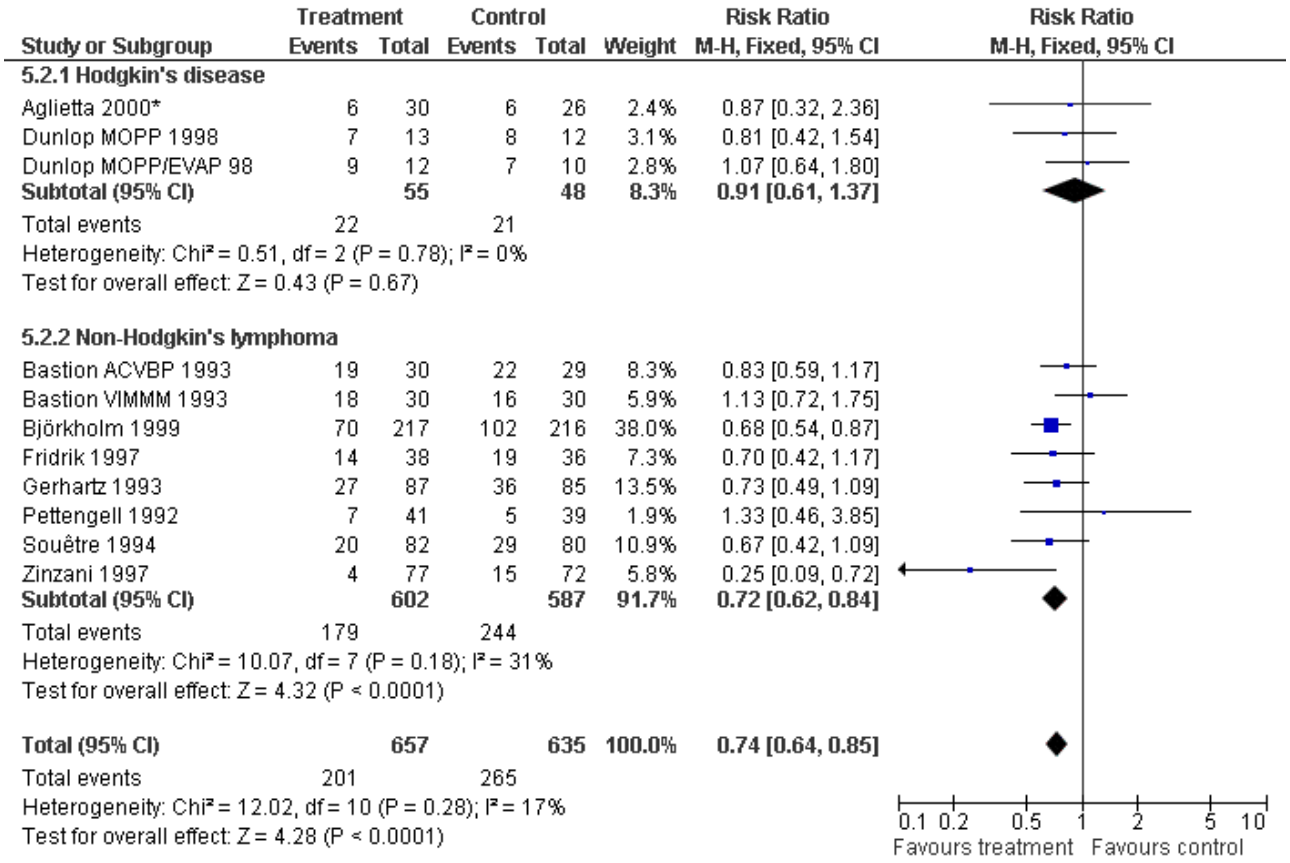


Figure 33. Forest plot of comparison: 4 Sensitivity analysis: Infection, outcome: 4.3 Age.

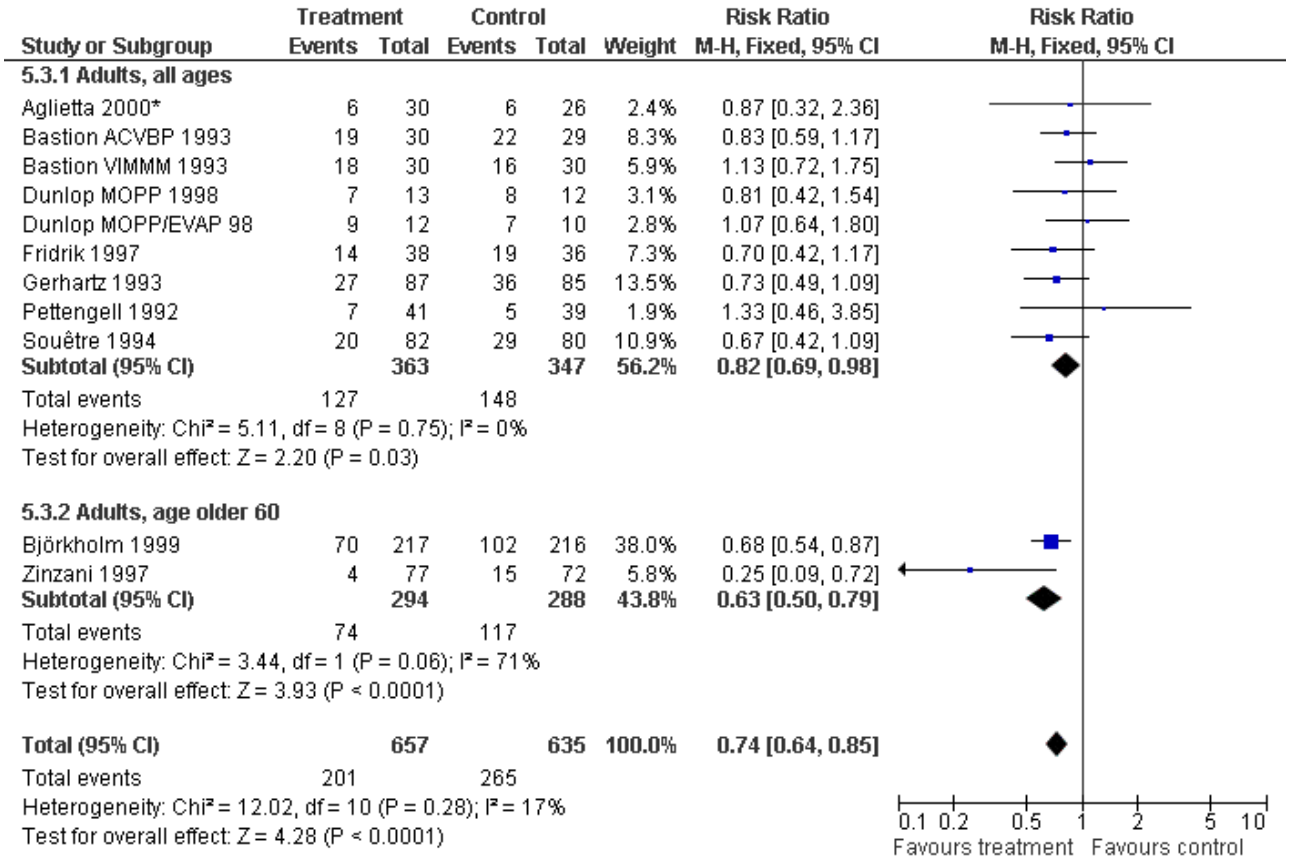


Figure 34. Forest plot of comparison: 4 Sensitivity analysis: Infection, outcome: 4.4 Use of antibiotic prophylaxis.

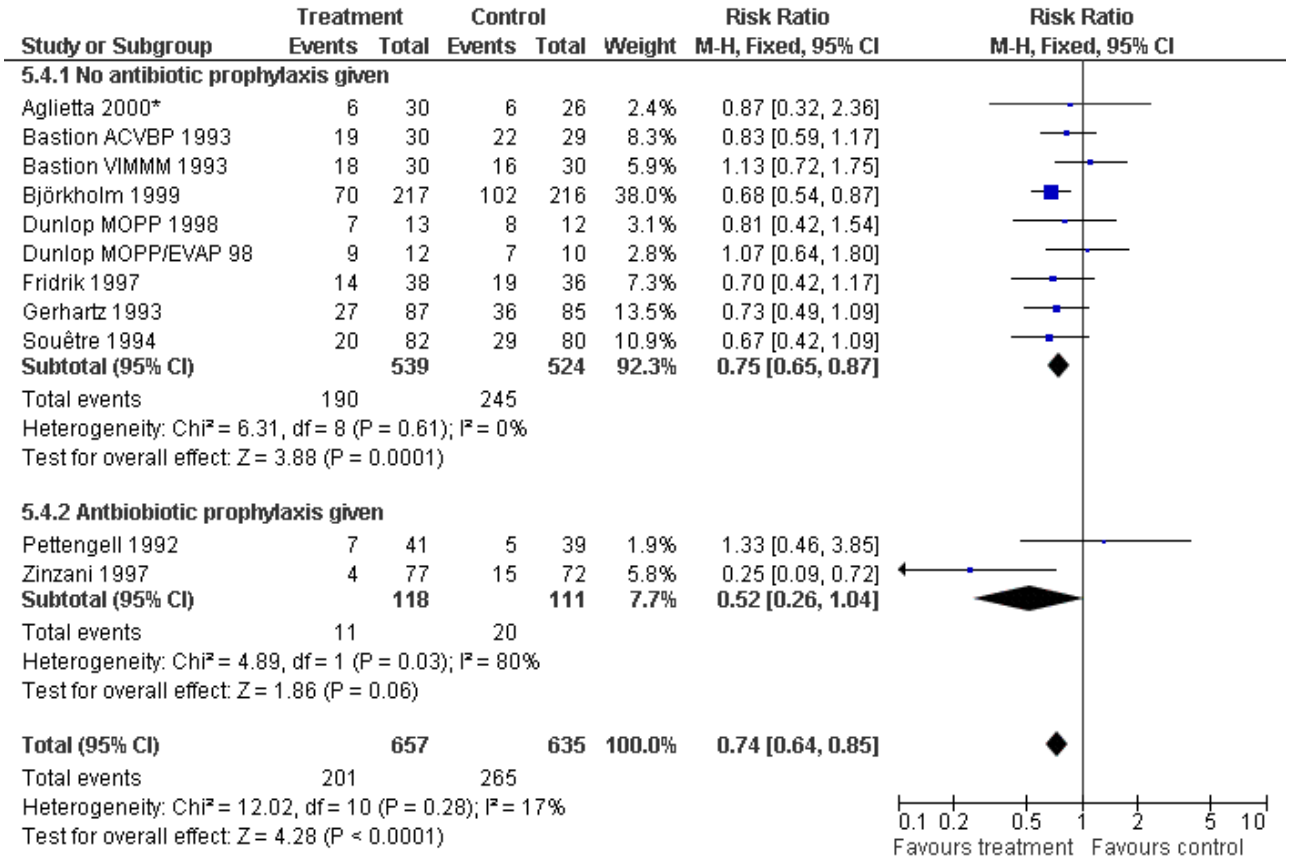


Figure 35. Forest plot of comparison: 4 Sensitivity analysis: Infection, outcome: 4.5 Blinded versus open label studies.

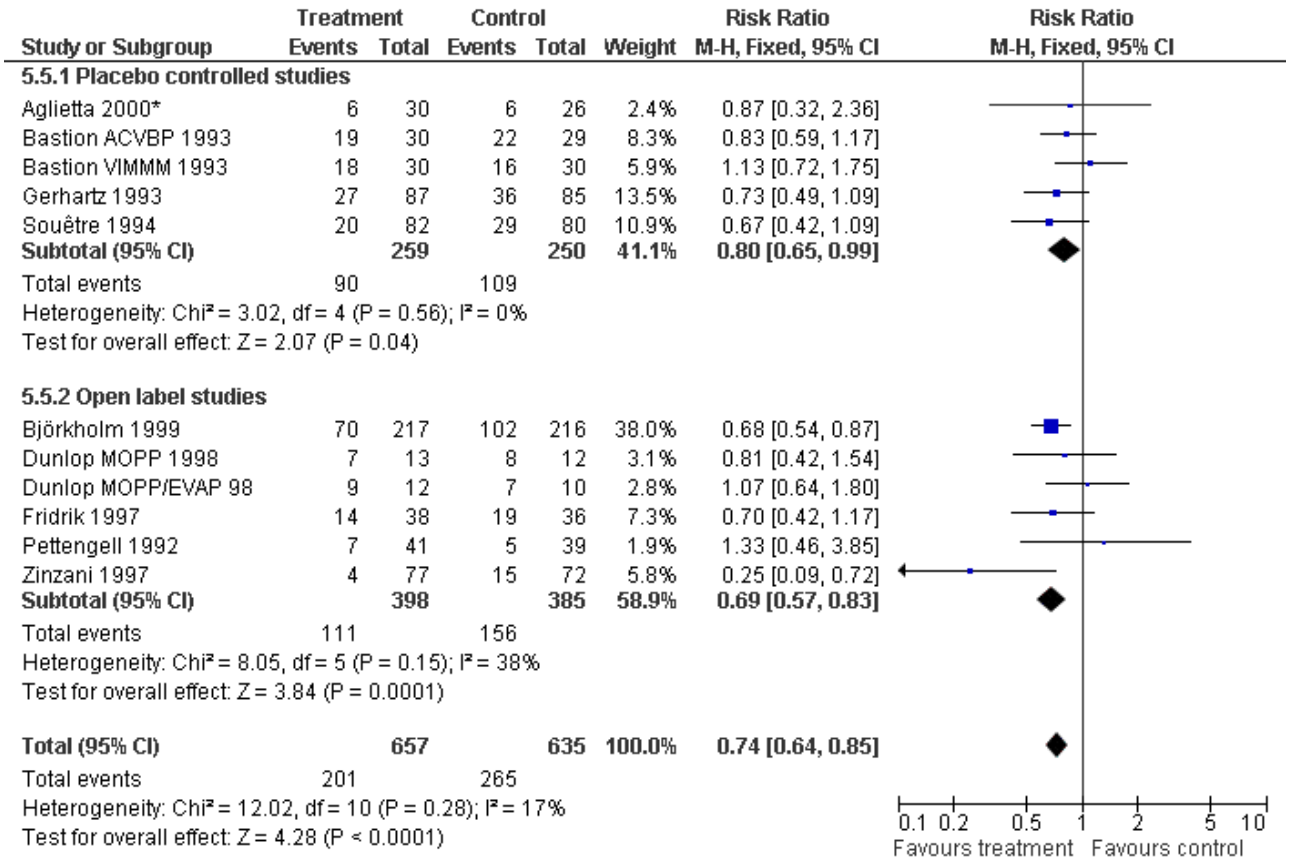


Figure 36. Forest plot of comparison: 4 Sensitivity analysis: Infection, outcome: 4.6 Concealed versus unclear method of allocation.

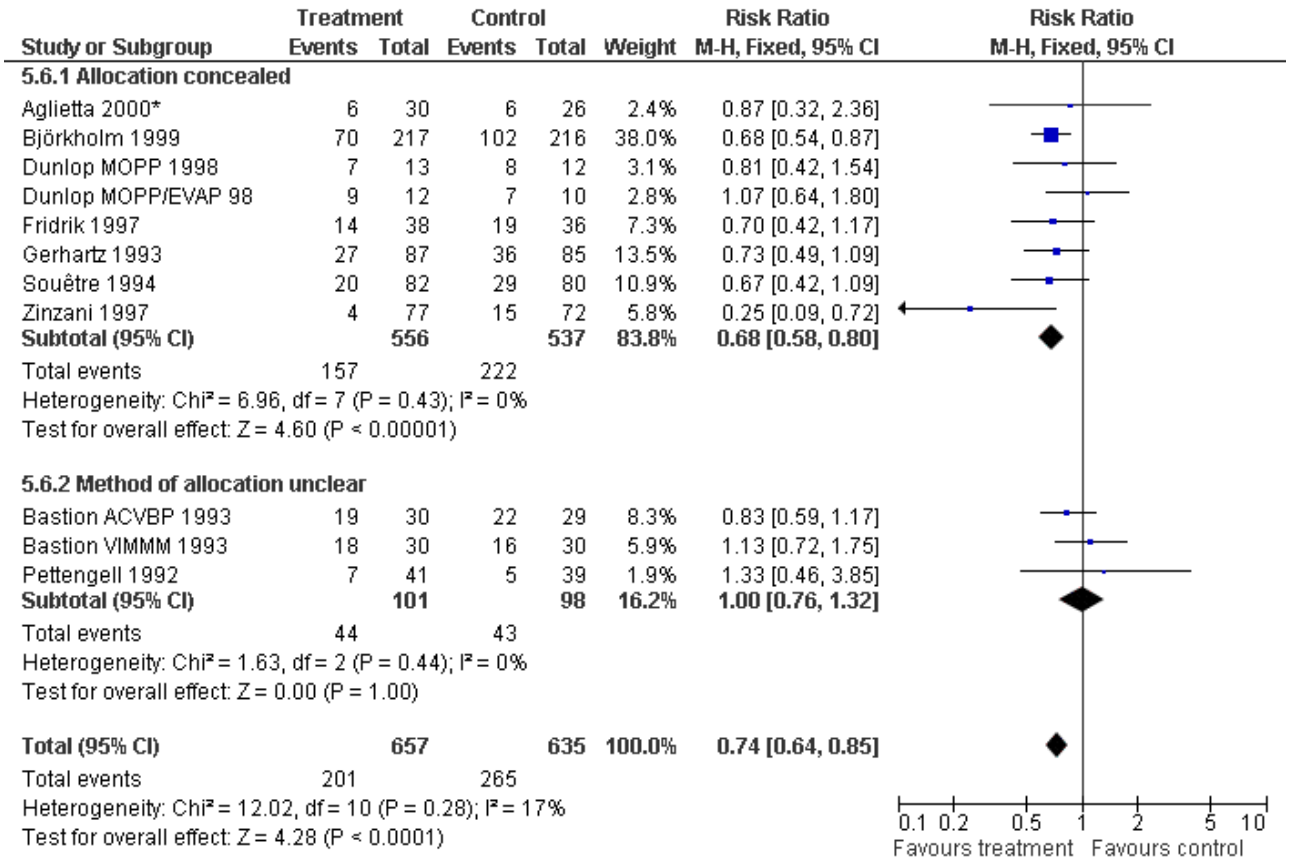


Figure 37. Forest plot of comparison: 4 Sensitivity analysis: Infection, outcome: 4.7 Published and reported data versus unpublished, unreported or abstract publications only.

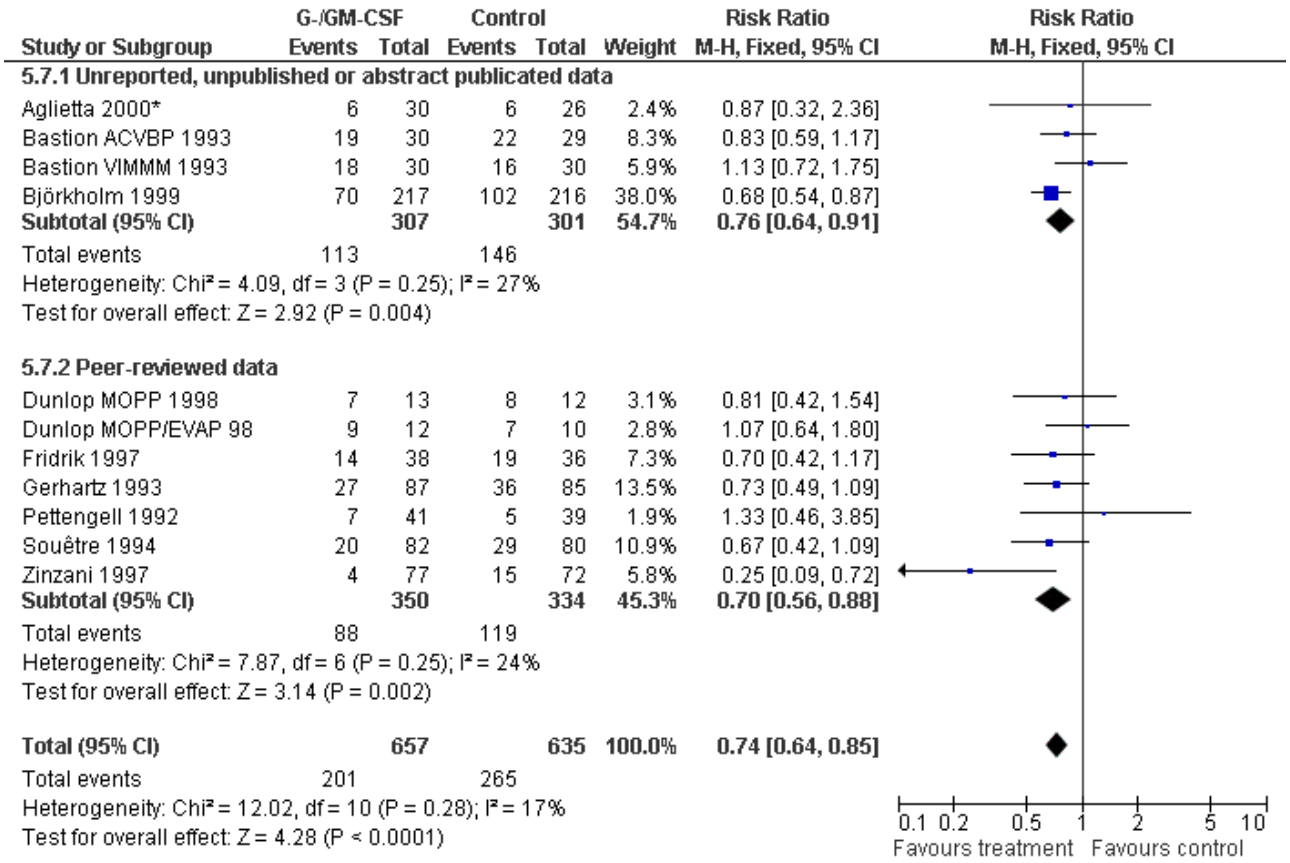


Figure 38. Forest plot of comparison: 4 Sensitivity analysis: Infection, outcome: 4.8 Size of study.

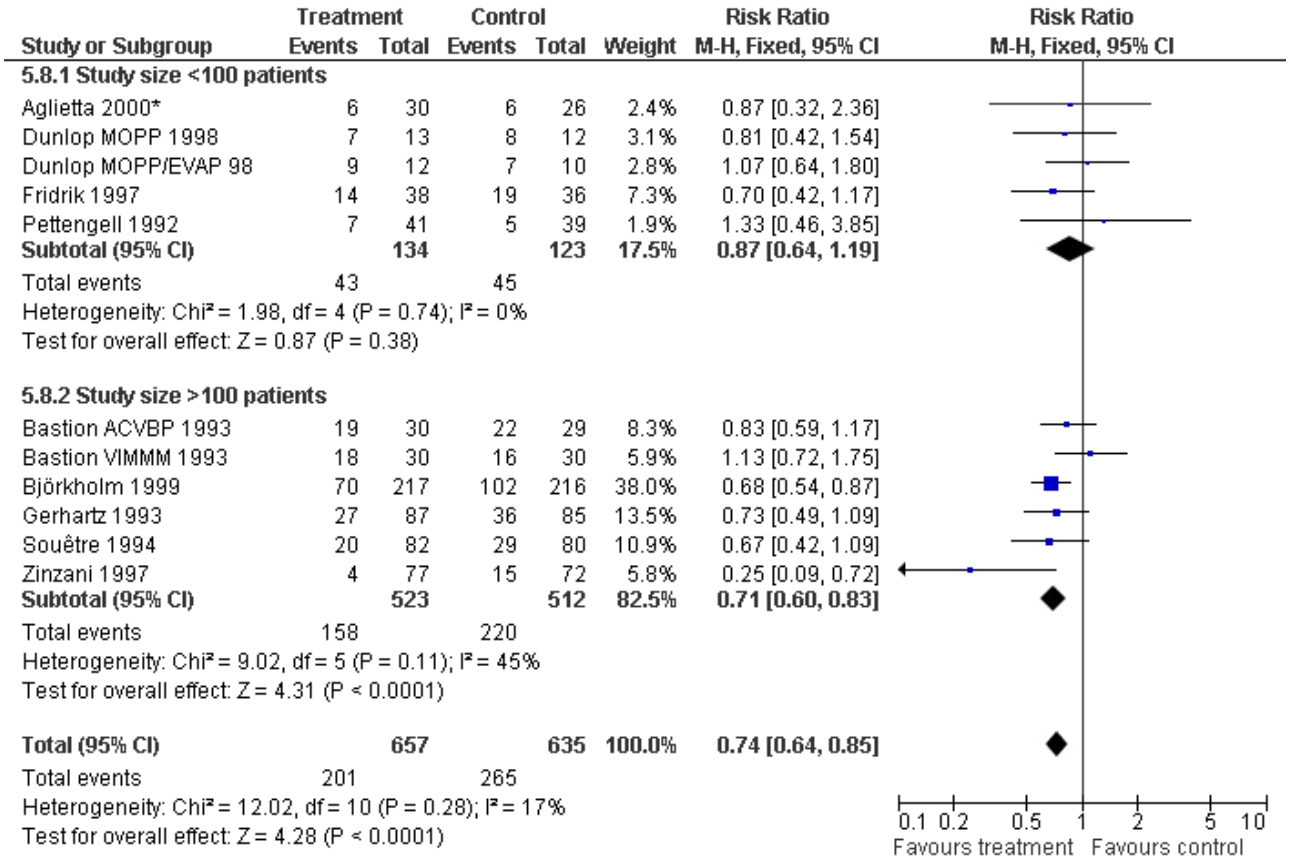
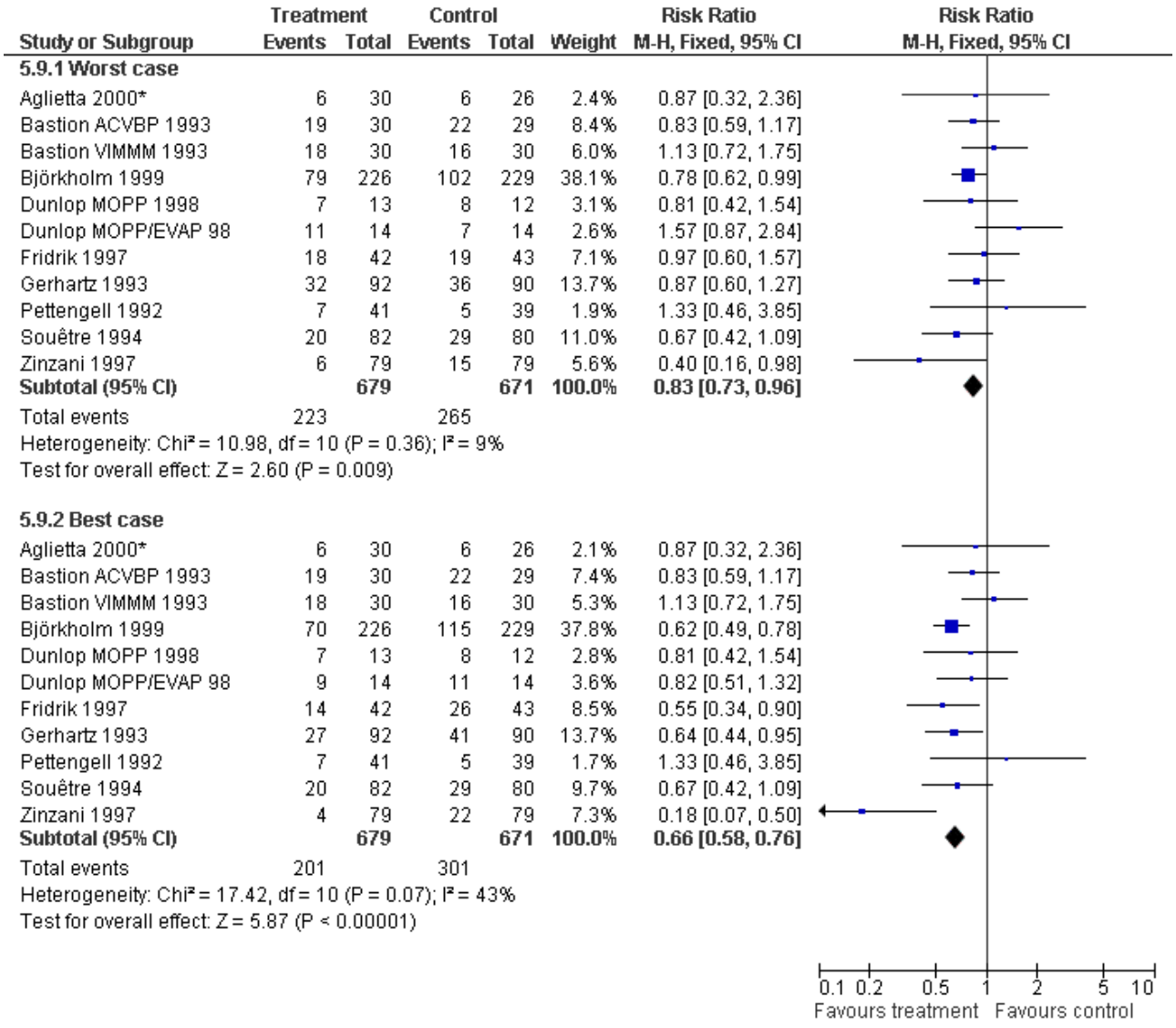


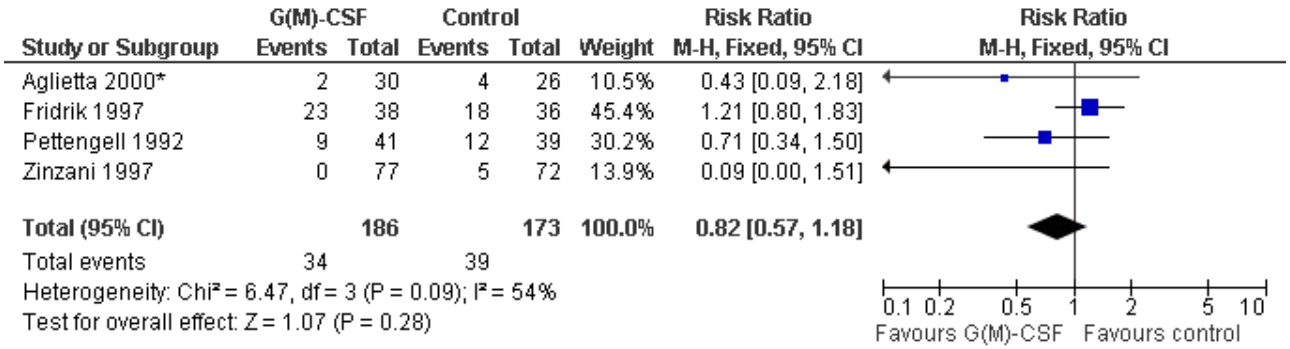
Figure 39. Forest plot of comparison: 4 Sensitivity analysis: Infection, outcome: 4.9 Worst case-best case.



Parenteral antibiotic treatment

Data from four studies including 359 patients were pooled in this analysis (Pettengell 1992; Fridrik 1997; Zinzani 1997; Aglietta 2000*). The risk of requiring parenteral antibiotic treatment was reduced by 18% in the G-CSF and GM-CSF treated groups (RR 0.82; 95 % CI 0.57 to 1.18), but this was not statistically significant; see Figure 40. There was no significant statistical heterogeneity among the trials (chi squared = 9.12, df = 4, P = 0.058). A test for publication bias (P = 0.026) indicated that both the RR and its 95% CI may be overestimated.

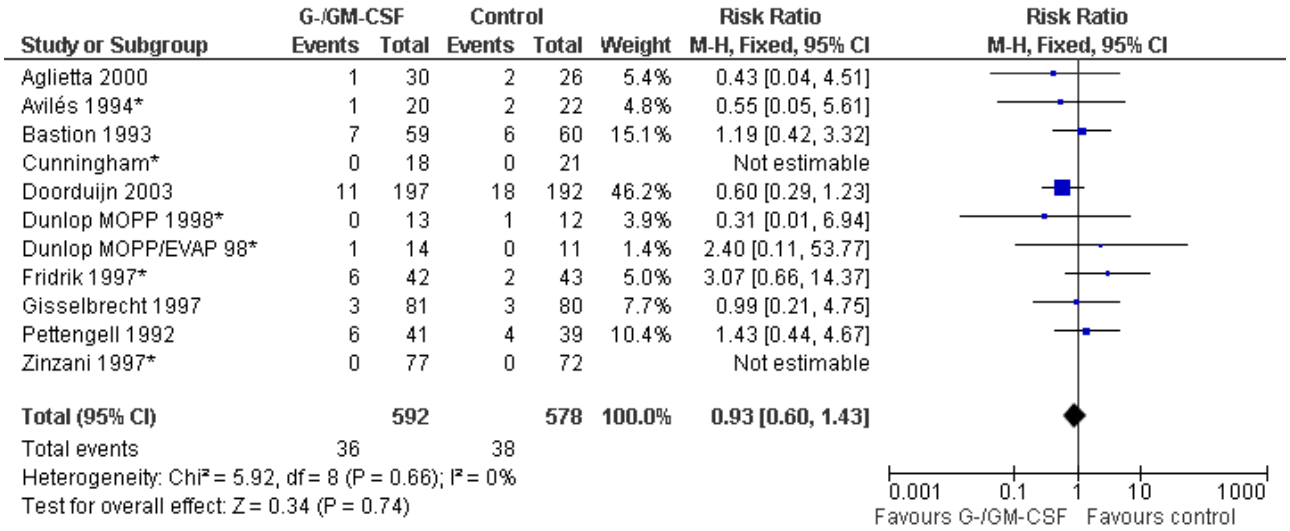
Figure 40. Forest plot of comparison: 1 G-CSF/GM-CSF versus control, outcome: 1.5 Parenteral antibiotic treatment.



Mortality during chemotherapy

Ten studies (one with two chemotherapy regimens) with 1170 patients were included in the analysis. Overall, 36 out of 592 patients treated with G-CSF or GM-CSF and 38 out of 975 patients in the control group died during chemotherapy (RR 0.93; 95% CI 0.60 to 1.43) (Cunningham*; Pettengell 1992; Bastion 1993; Avilés 1994*; Fridrik 1997*; Gisselbrecht 1997; Zinzani 1997; Dunlop MOPP/EVAP 98*; Dunlop MOPP 1998 ; Aglietta 2000; Doorduijn 2003; Burton 2006). There was no significant statistical heterogeneity among the trials (chi squared = 5.92, df = 8 , P = 0.66); see Figure 41.

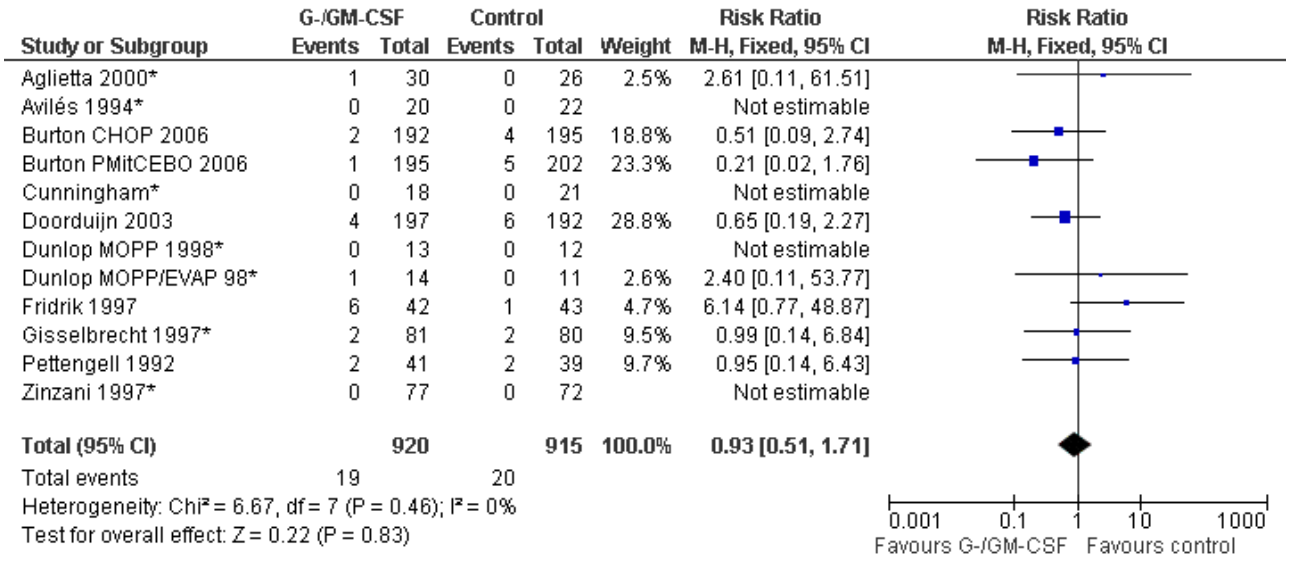
Figure 41. Forest plot of comparison: 1 G-CSF/GM-CSF versus control, outcome: 1.6 Overall mortality during chemotherapy.



Infection related mortality during chemotherapy

Ten studies (one with two chemotherapy regimens) with 1835 patients were included in the analysis of infection related mortality during chemotherapy. Nineteen out of 920 patients treated with G-CSF or GM-CSF and twenty out of 915patients in the control group died of infection during treatment (RR 0.93; 95% CI 0.51 to 1.71) (Cunningham*; Pettengell 1992; Avilés 1994*; Fridrik 1997; Gisselbrecht 1997*; Zinzani 1997*; Dunlop MOPP 1998*; Dunlop MOPP/EVAP 98*; Aglietta 2000*; Doorduijn 2003; Burton 2006), but this was not statistically significant. There was no significant statistical heterogeneity among the trials (chi squared = 6.67, df = 7, P = 0.46); see Figure 42. Overall, there is no evidence that G-CSF or GM-CSF affect overall mortality and infection related mortality during chemotherapy.

Figure 42. Forest plot of comparison: 1 G-CSF/GM-CSF versus control, outcome: 1.7 Infection related mortality during chemotherapy.



Complete response

Analysis of complete tumour response was based on 11 trials including 2368 patients (Cunningham*; Avilés 1994; Engelhard 1994; Fridrik 1997; Gisselbrecht 1997; Zinzani 1997; Dunlop MOPP 1998*; Dunlop MOPP/EVAP 98*; Aglietta 2000; Ösby 2003; Doorduijn 2003; Burton 2006). Two trials, Dunlop 1998 and Ösby 2003 , were analysed by chemotherapy regimen. The overall risk of achieving complete response for patients treated with G-CSF or GM-CSF was increased by 3% (RR 1.03; 95% CI 0.95 to 1.10), but this was not statistically significant; see Figure 43. There was no significant heterogeneity among the trials (chi squared = 9.84, df = 12, P = 0.63). The test for small study bias was significant (P = 0.02624), indicating that the effect of G-CSF or GM-CSF may be overestimated (see Figure 44) . A subgroup analysis of study size showed a bigger treatment effect in small studies (RR 1.31; 95% CI 1.08 to 1.60) compared to large studies (RR 0.99; 95% CI 0.92 to 1.07), P value for difference between subgroups: 0.0154; see Figure 45, comparison 6.7. Other sensitivity analyses (type of drug, tumour entity, patient age, antibiotic prophylaxis, quality of study and publication type; comparison 6) did not show any significant differences (Figure 46; Figure 47; Figure 48; Figure 49; Figure 50; Figure 51).

Figure 43. Forest plot of comparison: 1 G-CSF/GM-CSF versus control, outcome: 1.8 Complete response.

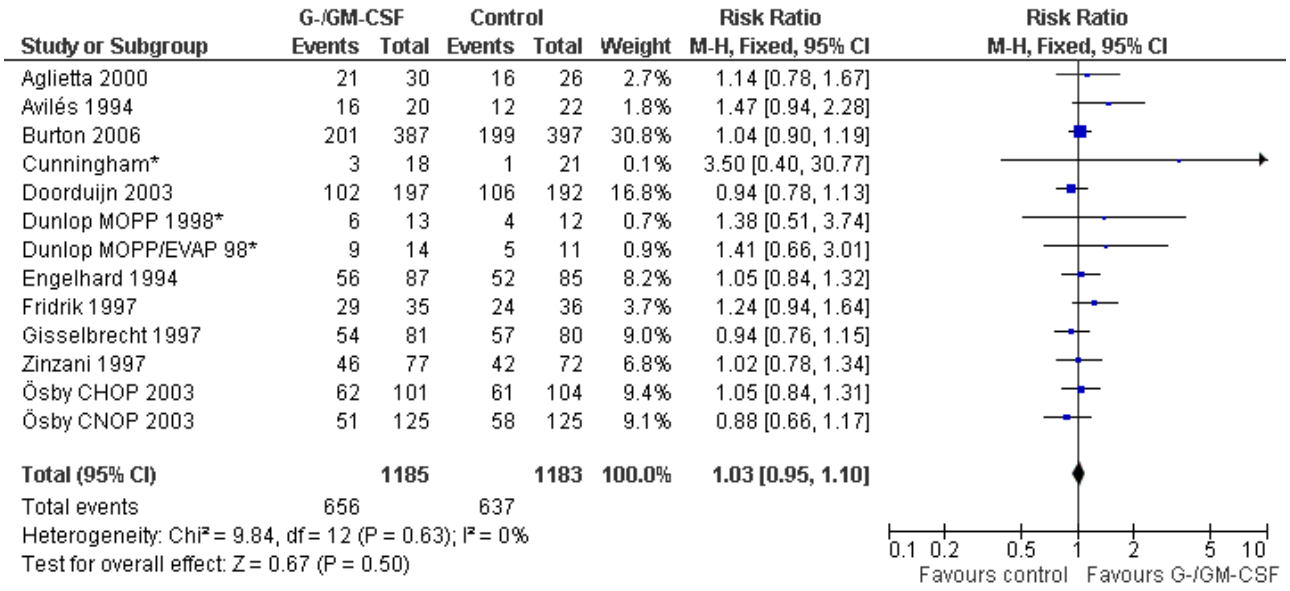


Figure 44. Forest plot of comparison: 5 Sensitivity analysis: Complete response, outcome: 5.1 GM-CSF versus G-CSF.

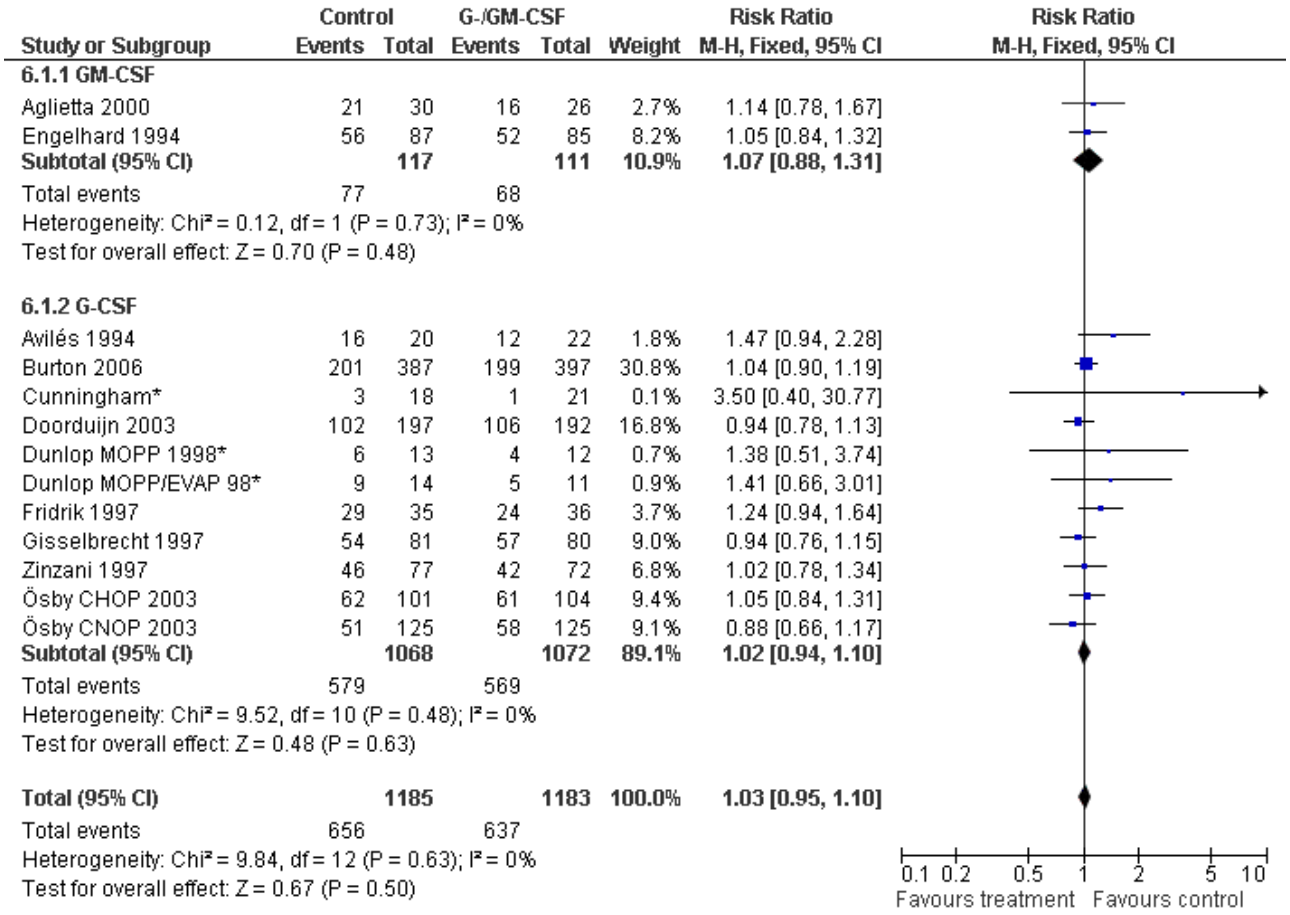


Figure 45. Forest plot of comparison: 5 Sensitivity analysis: Complete response, outcome: 5.7 Size of studies.

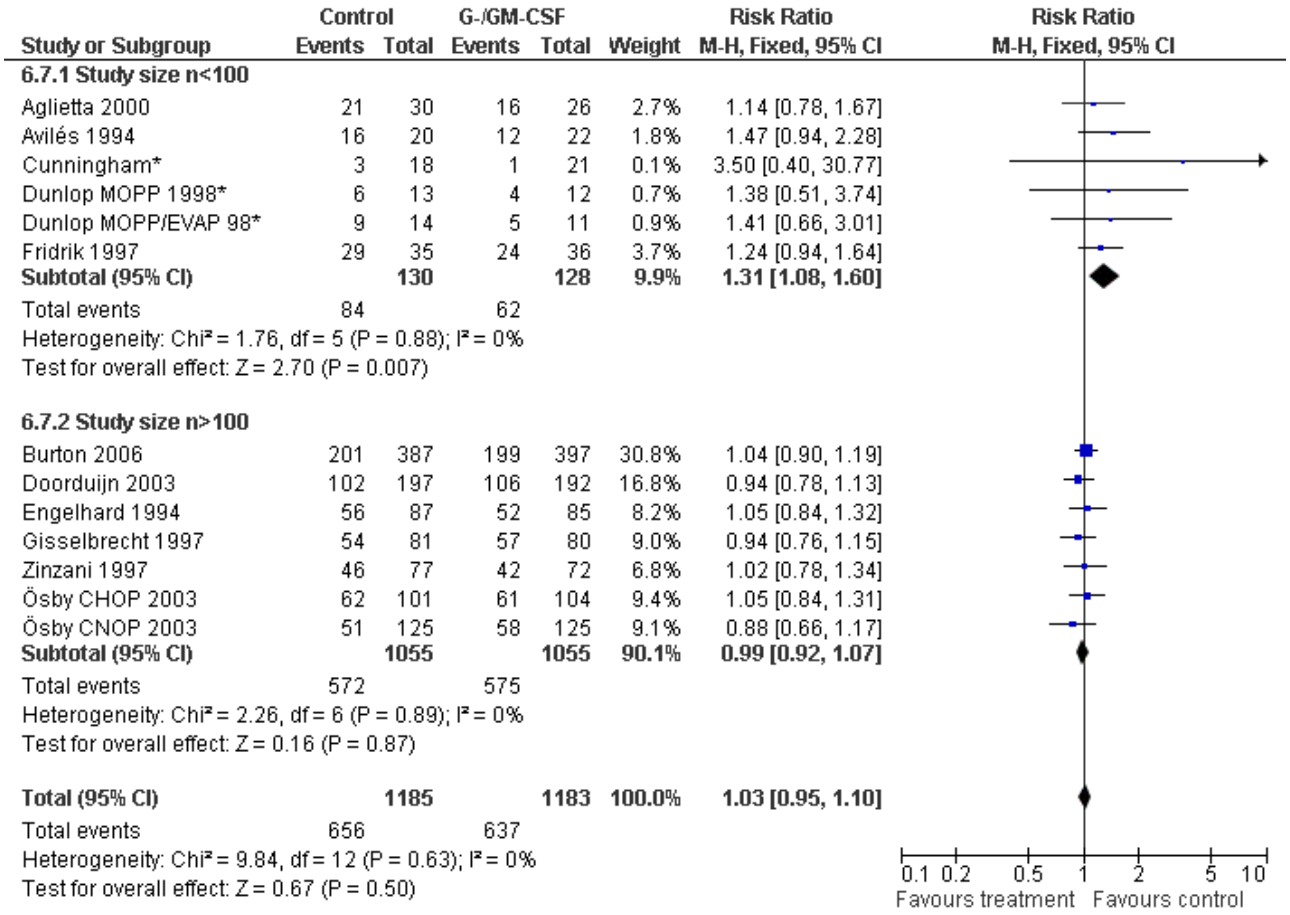


Figure 46. Forest plot of comparison: 5 Sensitivity analysis: Complete response, outcome: 5.2 HD versus NHL.

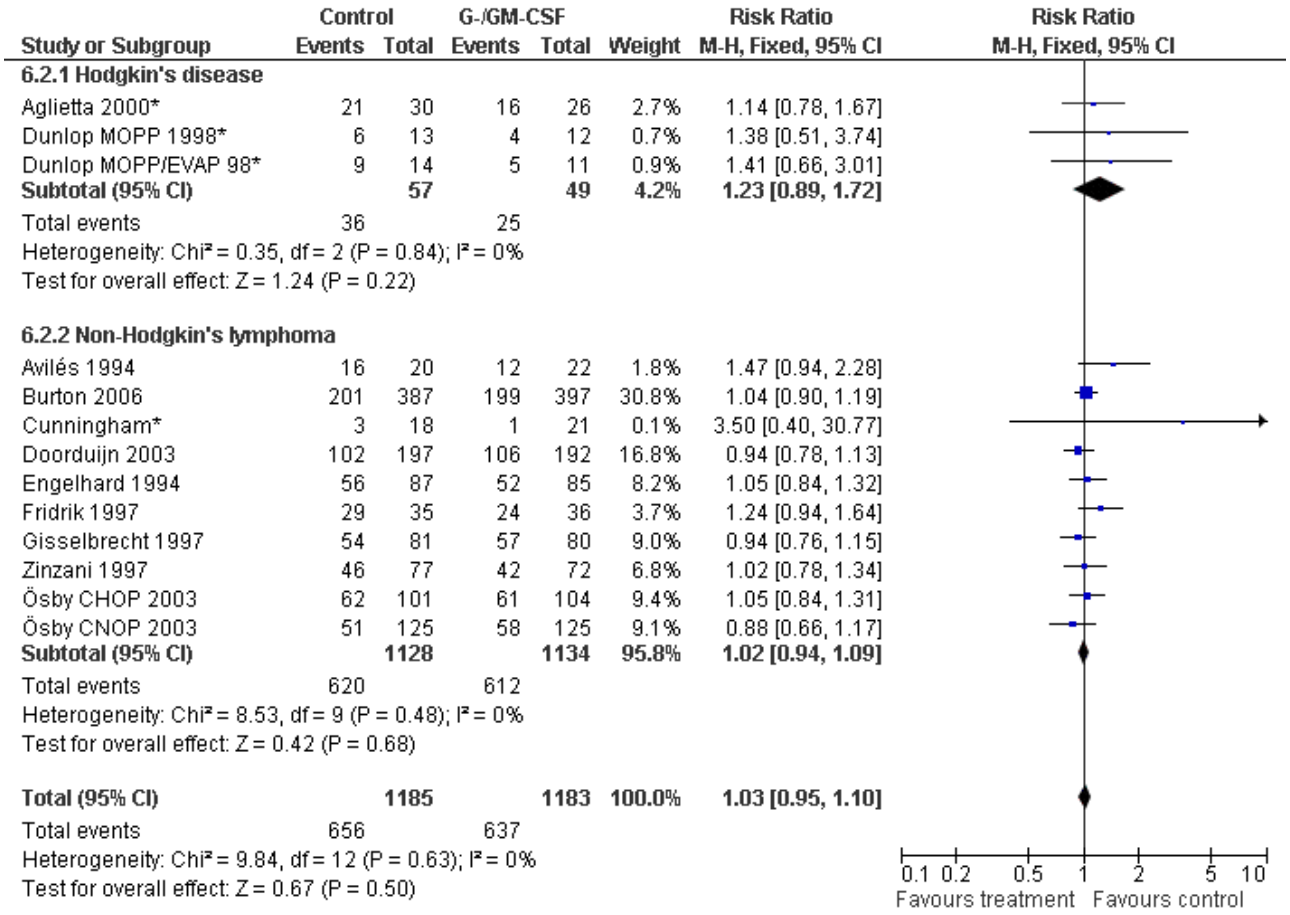


Figure 47. Forest plot of comparison: 5 Sensitivity analysis: Complete response, outcome: 5.3 Age.

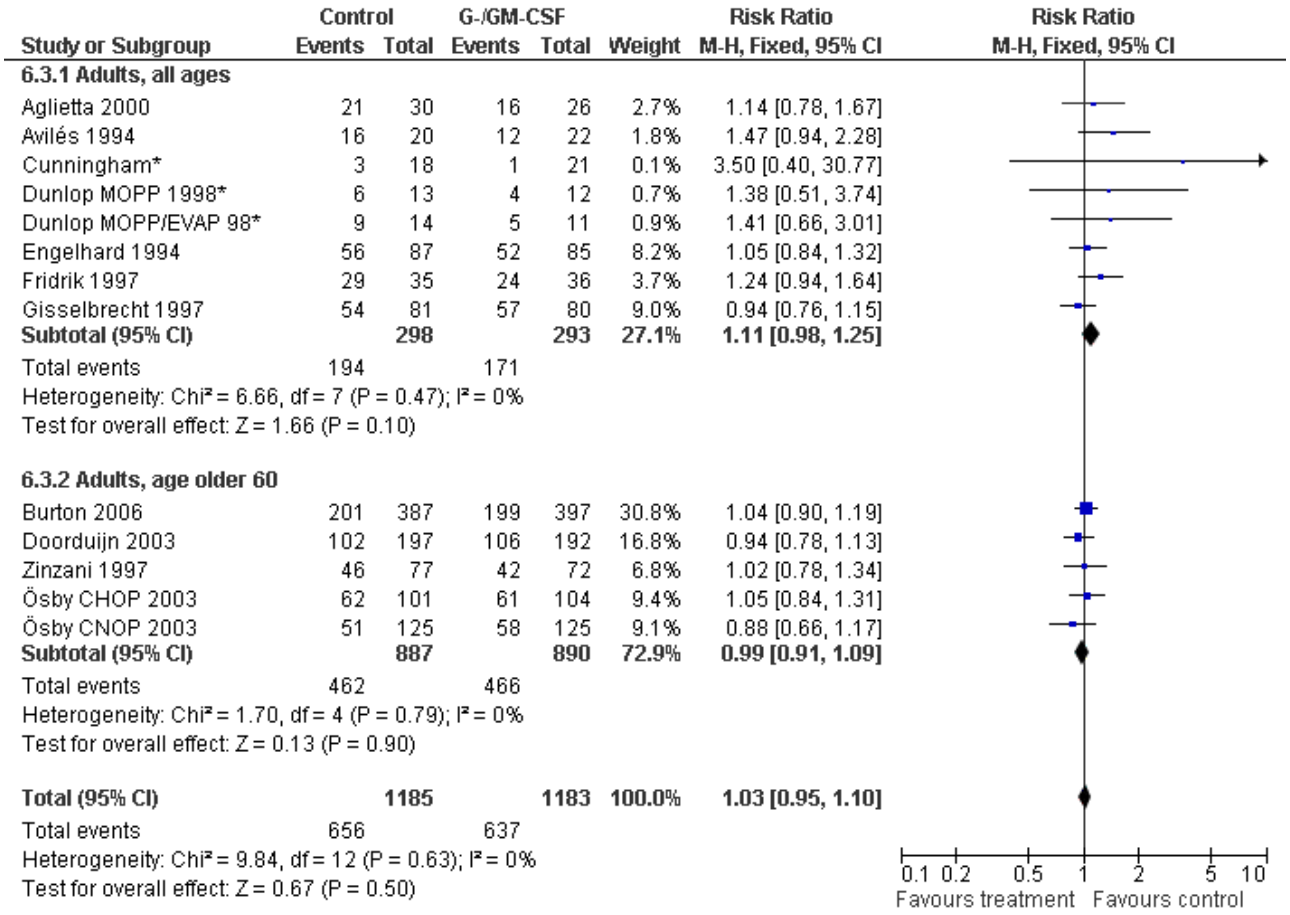


Figure 48. Forest plot of comparison: 5 Sensitivity analysis: Complete response, outcome: 5.4 Use of antibiotic prophylaxis.

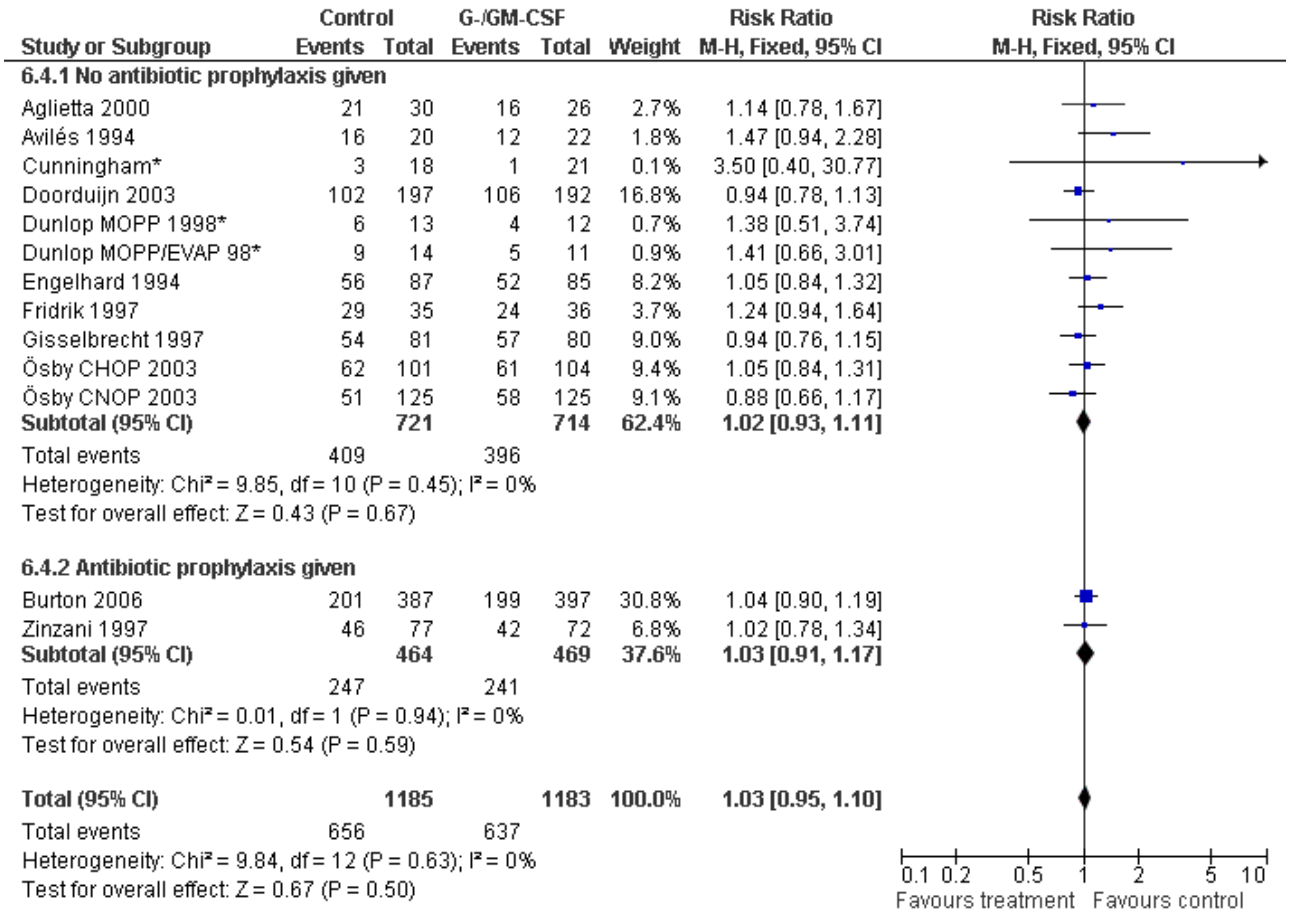


Figure 49. Forest plot of comparison: 5 Sensitivity analysis: Complete response, outcome: 5.5 Blinded versus open label studies.

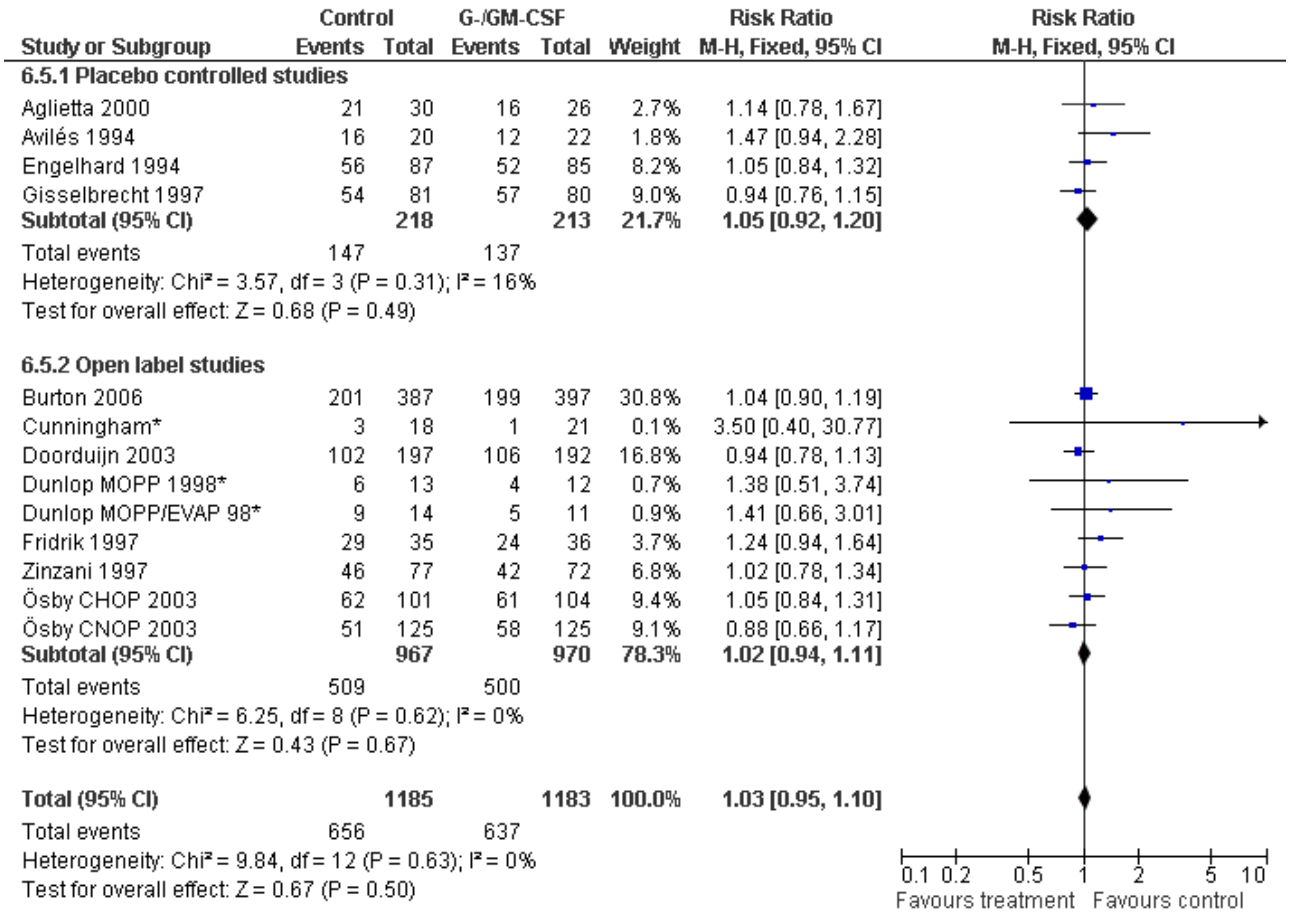


Figure 50. Forest plot of comparison: 5 Sensitivity analysis: Complete response, outcome: 5.6 Published and reported data versus unpublished or unreported data.

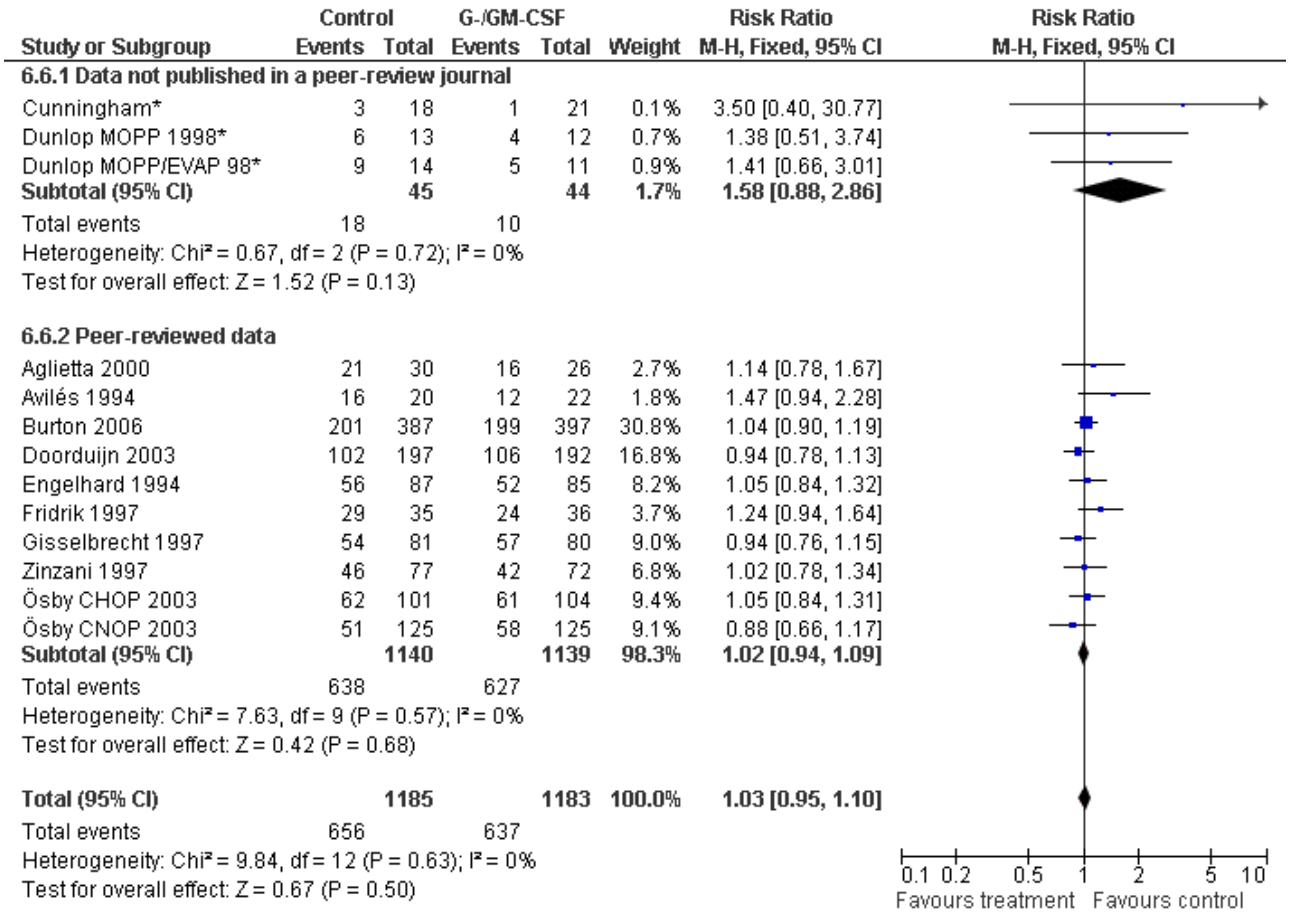
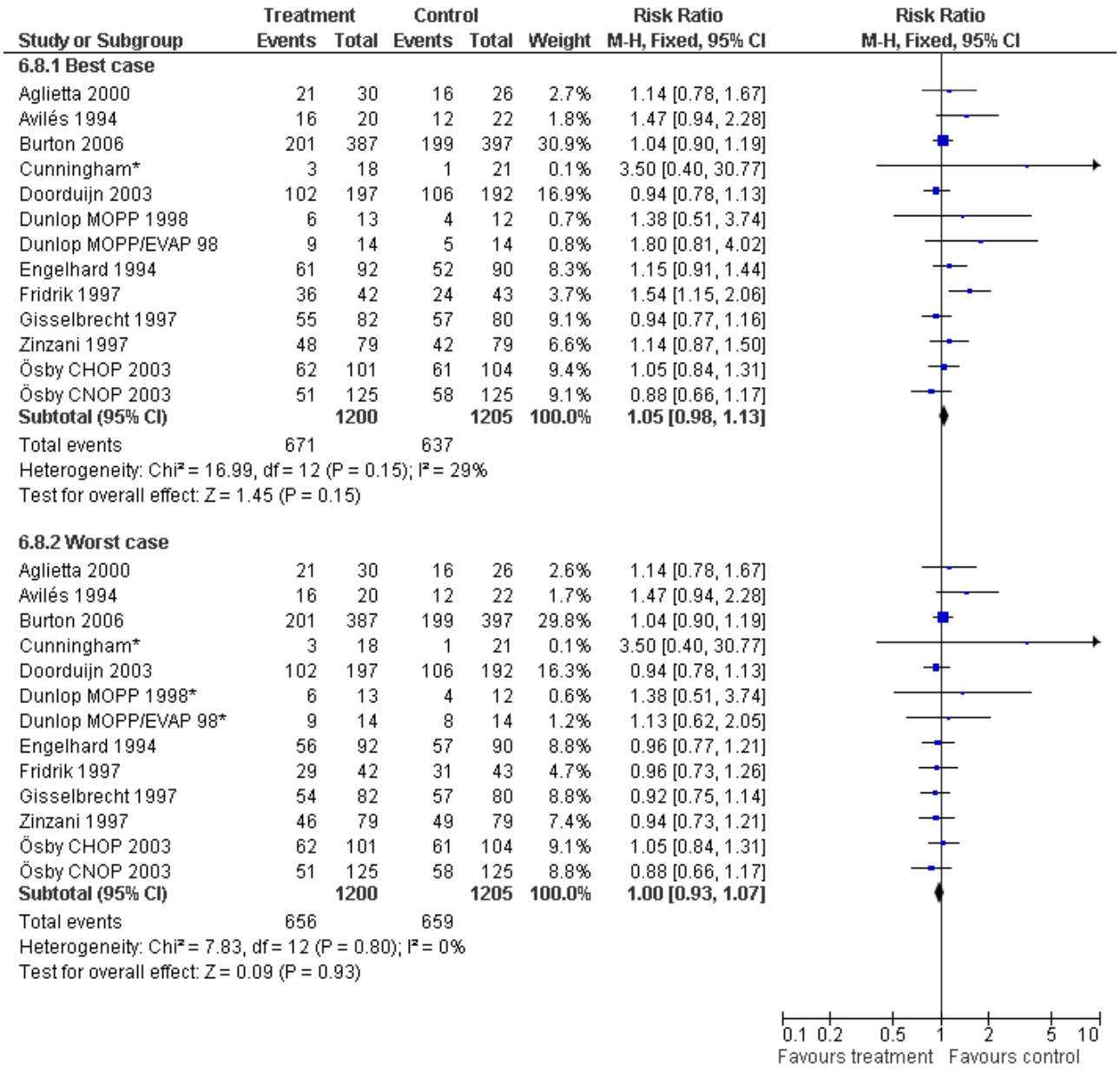


Figure 51. Forest plot of comparison: 5 Sensitivity analysis: Complete response, outcome: 5.8 Worst case - best case.



Adverse effects

Bone pain

Based on eight studies with 1204 patients, the risk of bone pain for patients treated with G-CSF or GM-CSF was more than doubled, compared to the control group (RR 3.57; 95% CI 2.09 to 6.12) (Pettengell 1992; Gerhartz 1993; Avilés 1994; Fridrik 1997; Gisselbrecht 1997; Zinzani 1997; Aglietta 2000; Ösby 2003). However, no patient withdrew from the study because of bone pain. There was no significant statistical heterogeneity among the trials (chi squared = 5.73, df = 8, P = 0.68); see Figure 52. Subgroup analysis (comparison 7) demonstrated a significantly (P = 0.026) smaller risk of bone pain for patients treated with GM-CSF (RR 1.37; 95% CI 0.54 to 3.47, 2 studies of N = 232), compared to patients receiving G-CSF (RR 5.33; 95% CI 2.66 to 10.68, 6 studies of N = 972); see Figure 53. However, this observation is based on indirect comparison. Sensitivity analysis for placebo-controlled or open studies, tumour entity, age of patients, quality and size of study did not show significant differences (Figure 54; Figure 55; Figure 56; Figure 57; Figure 58).

Figure 52. Forest plot of comparison: 1 G-CSF/GM-CSF versus control, outcome: 1.11 Adverse events: bone pain.

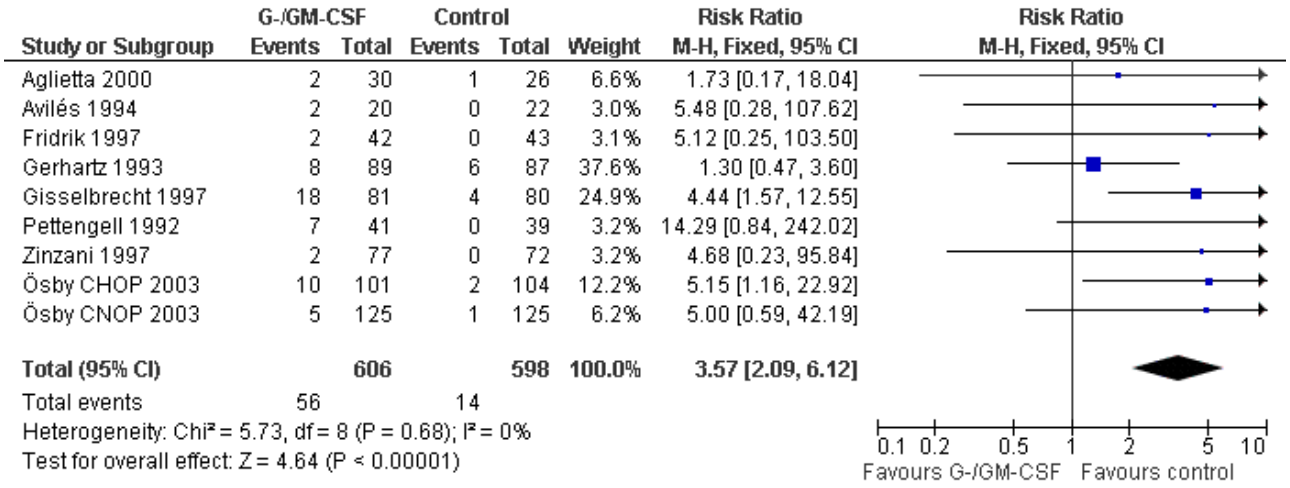


Figure 53. Forest plot of comparison: 7 Sensitivity analysis: Bone Pain, outcome: 7.1 GM-CSF versus G-CSF.

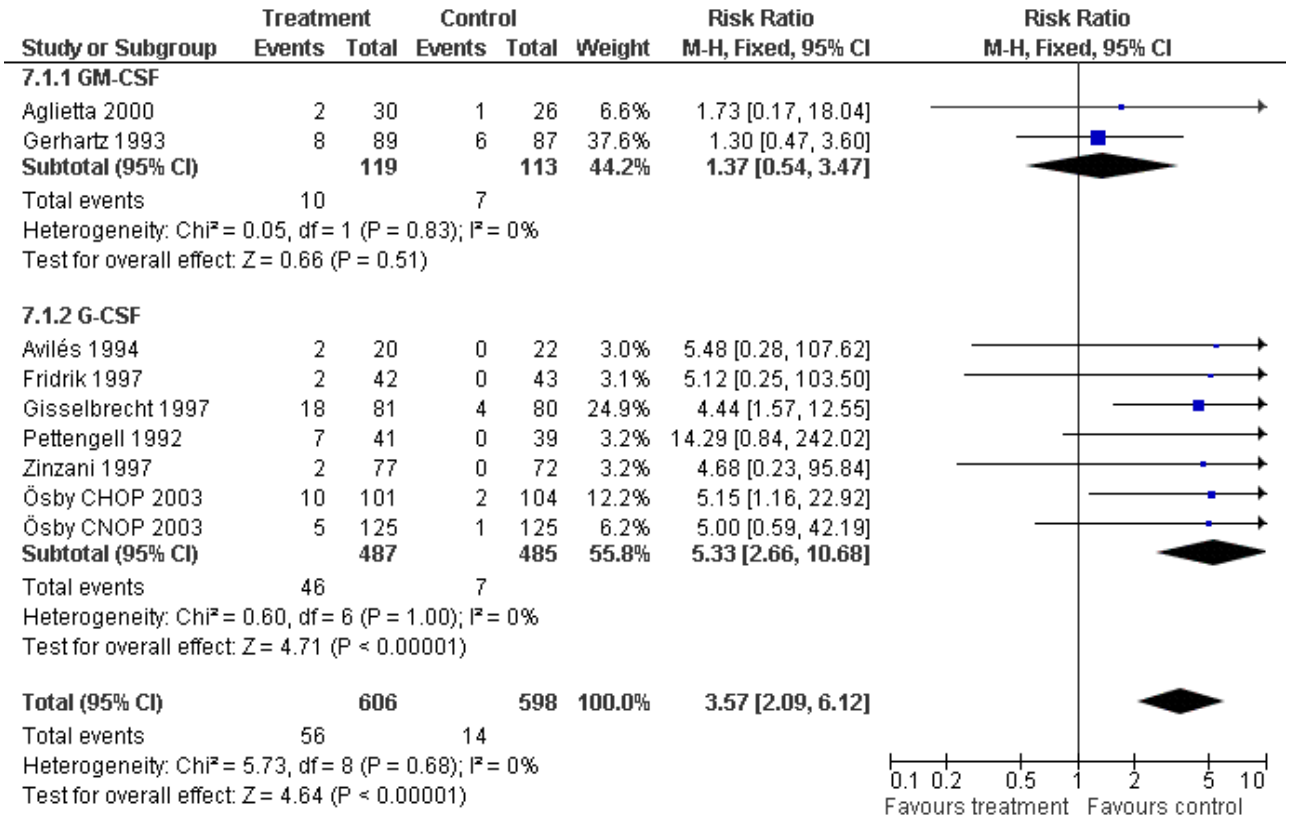


Figure 54. Forest plot of comparison: 7 Sensitivity analysis: Bone Pain, outcome: 7.2 HD versus NHL.

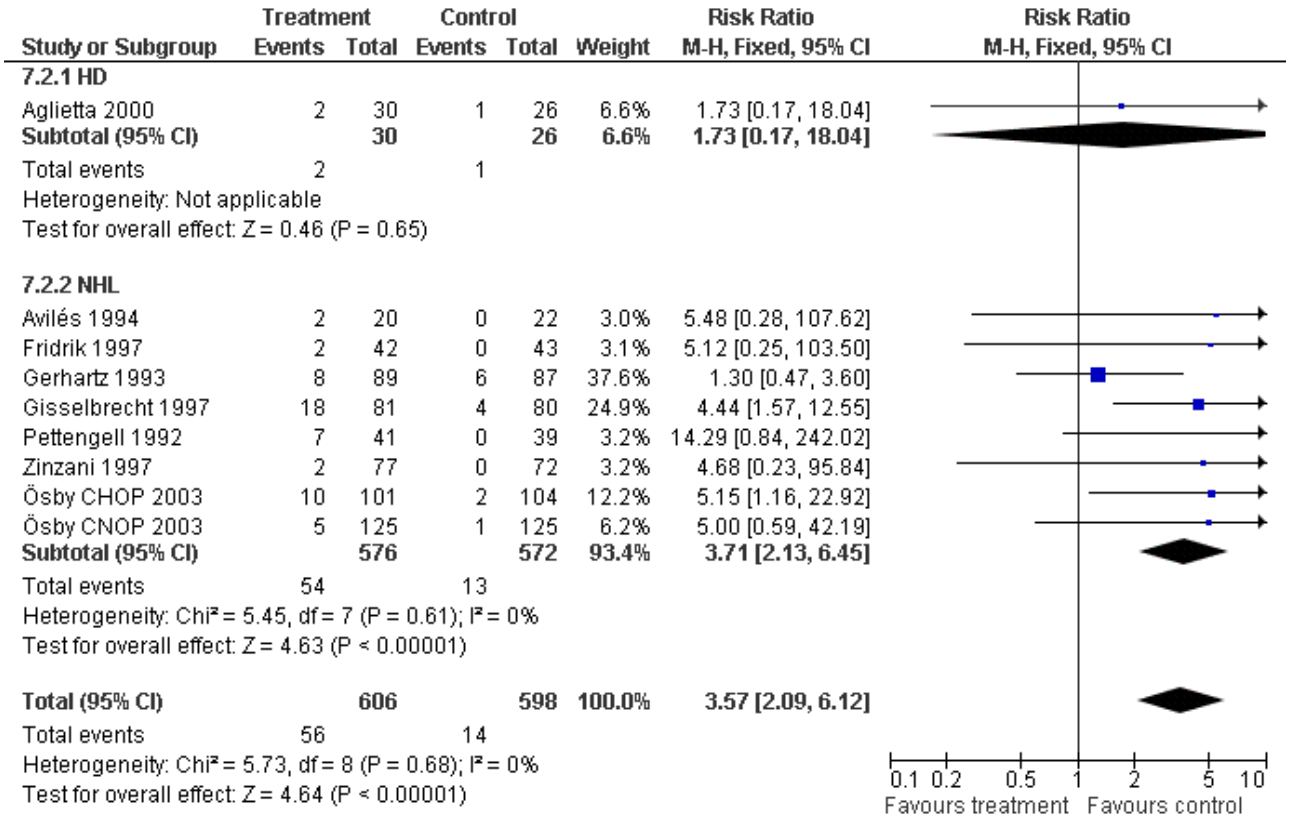


Figure 55. Forest plot of comparison: 7 Sensitivity analysis: Bone Pain, outcome: 7.3 Age.

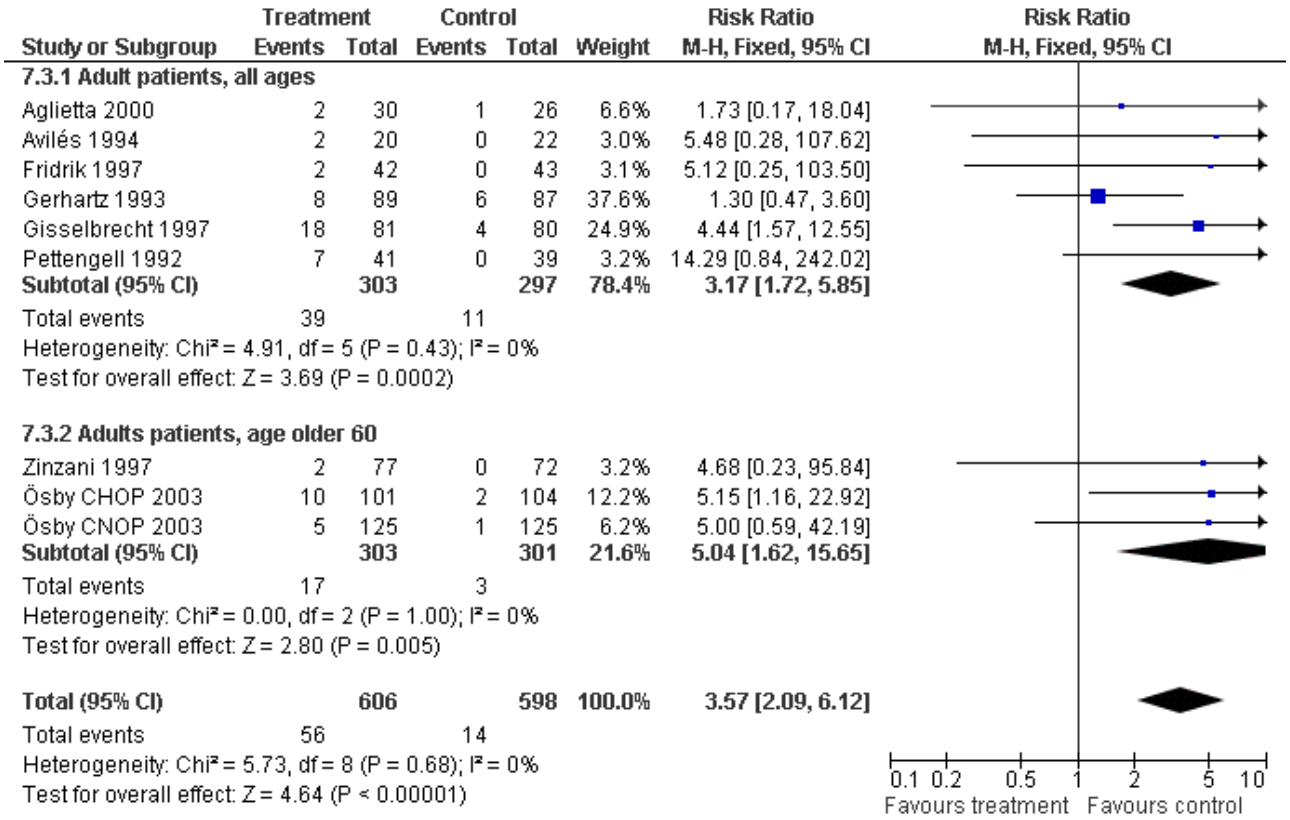


Figure 56. Forest plot of comparison: 7 Sensitivity analysis: Bone Pain, outcome: 7.4 Blinding.

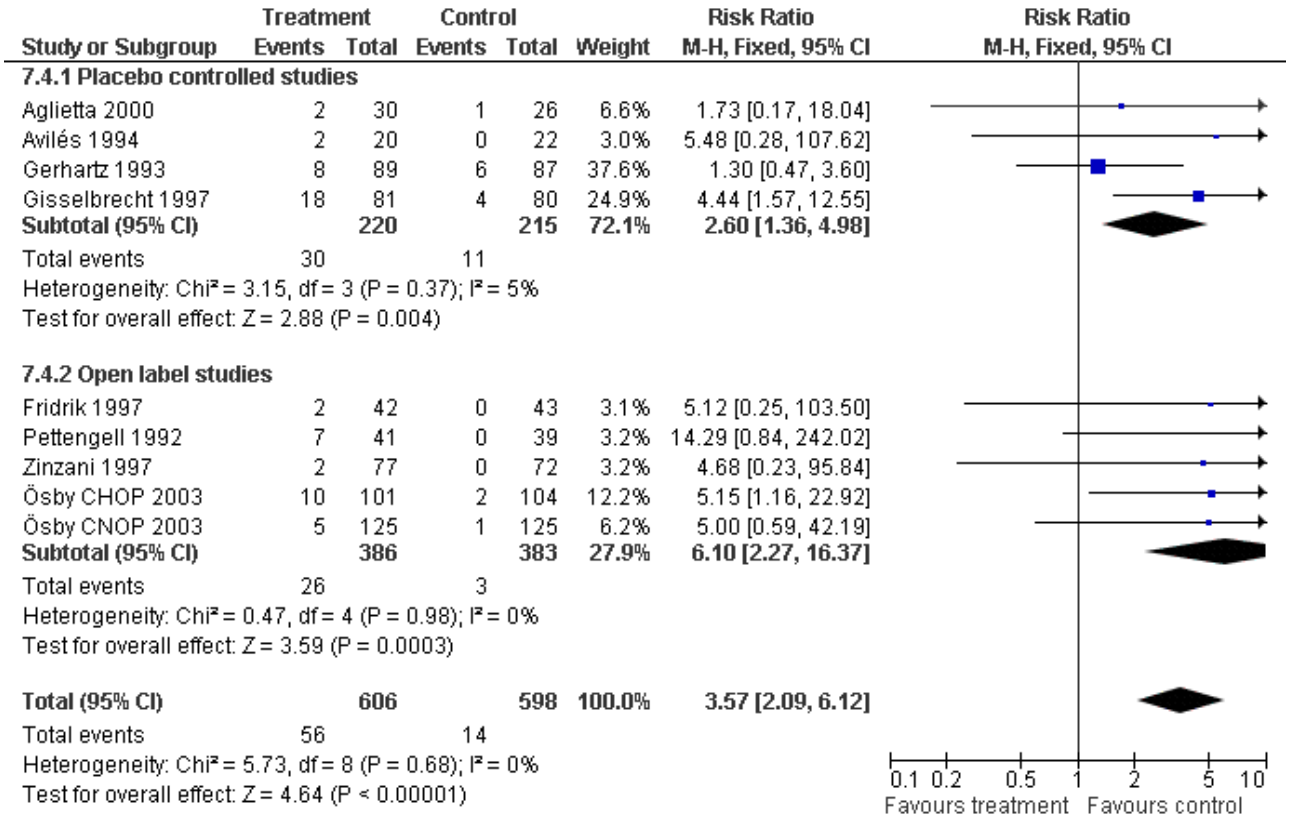


Figure 57. Forest plot of comparison: 7 Sensitivity analysis: Bone Pain, outcome: 7.5 Concealment of allocation.

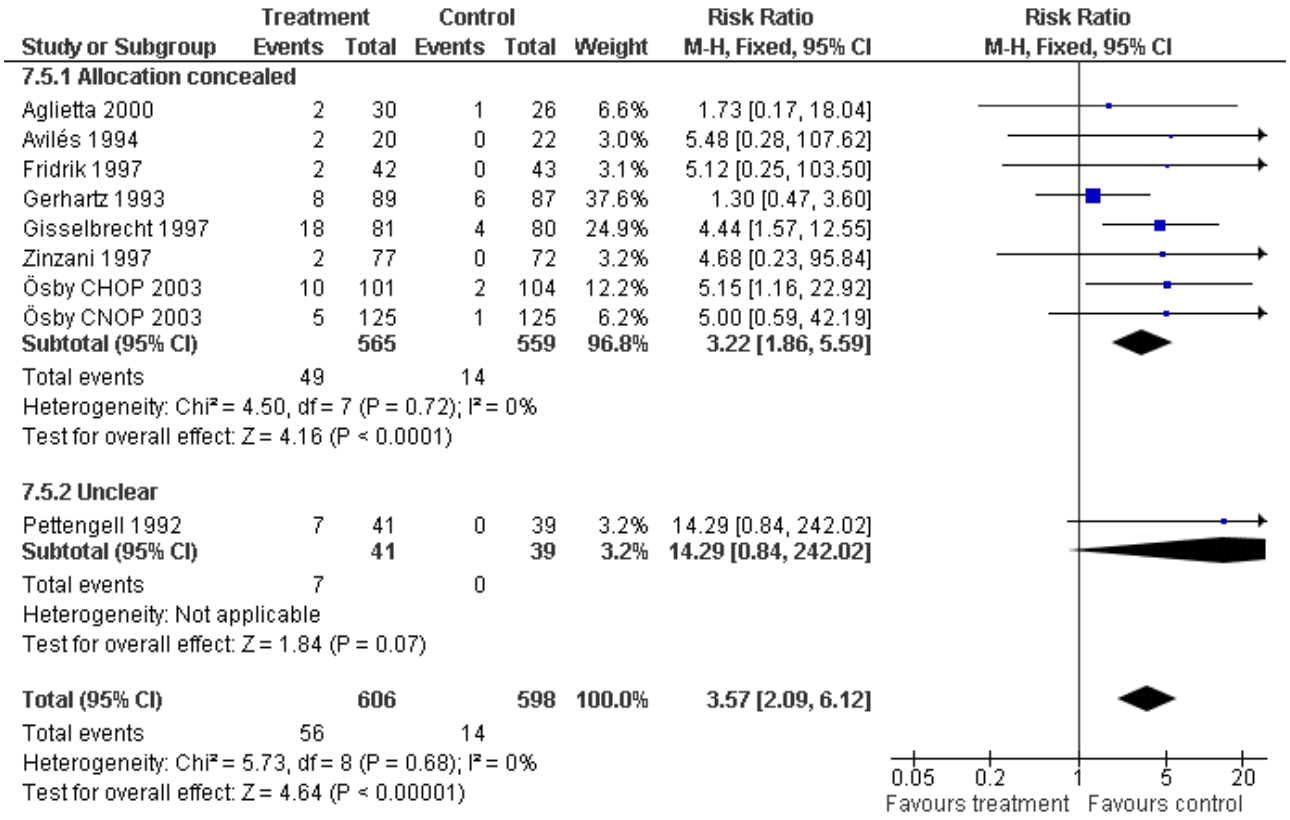
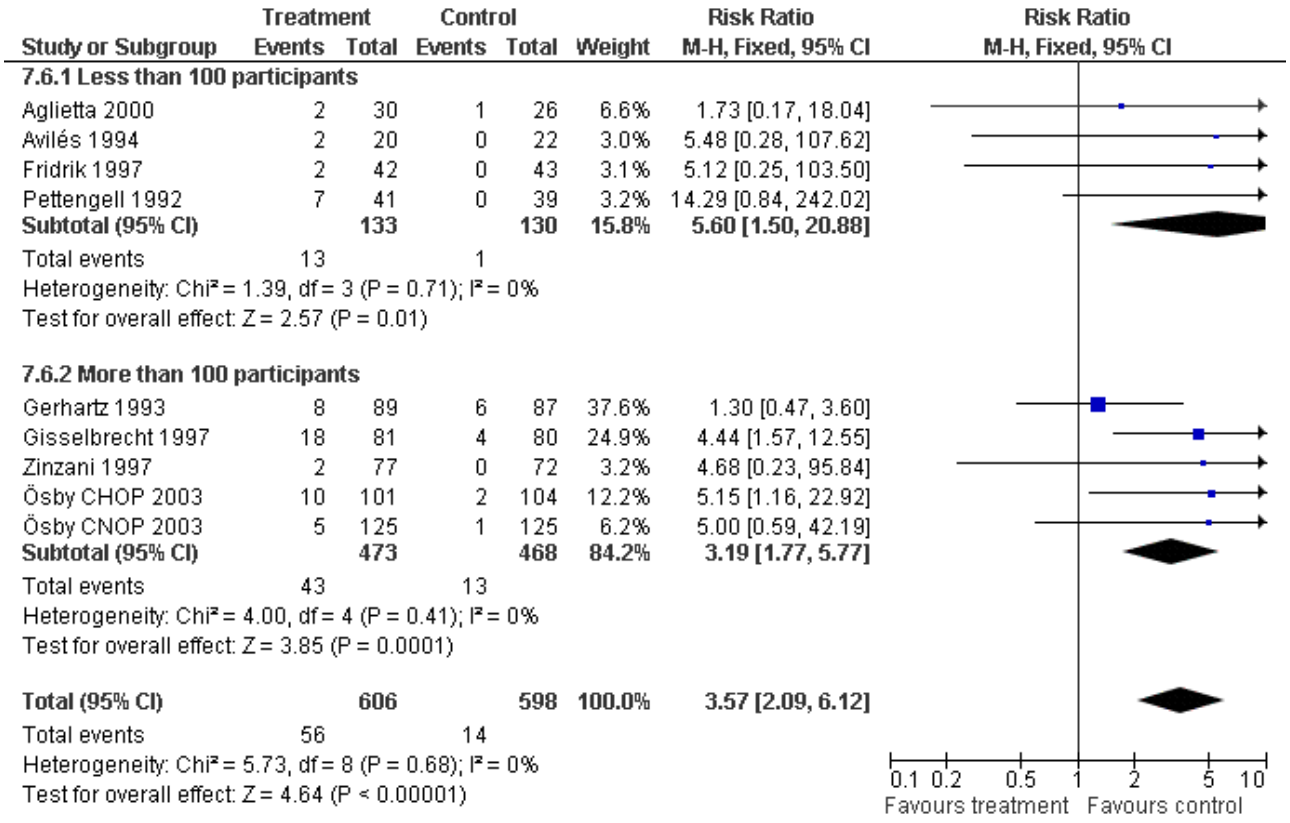


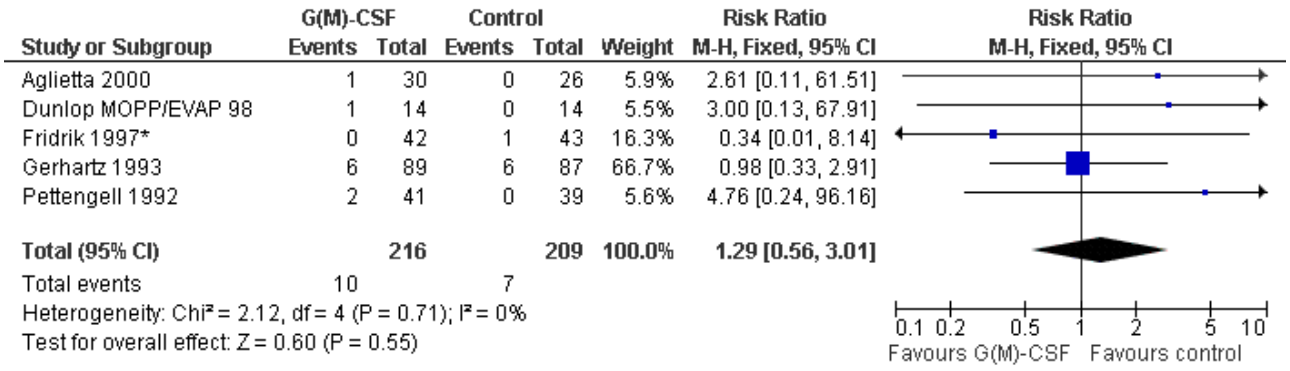
Figure 58. Forest plot of comparison: 7 Sensitivity analysis: Bone Pain, outcome: 7.6 Study size.



Thromboembolic complications

Based on 425 patients in 5 trials, a total of 17 thromboembolic complications were observed (RR 1.29; 95% CI 0.56 to 3.01) (Pettengell 1992; Gerhartz 1993; Fridrik 1997*; Dunlop MOPP/EVAP 98; Aglietta 2000); see Figure 59. There was no significant statistical heterogeneity among the trials (chi squared = 2.12, df = 4, P = 0.71). Thus, there is no evidence that G-CSF or GM-CSF increase the risk of thrombosis or related haemodynamic vascular complications such as transient ischaemic attacks, stroke or myocardial infarction.

Figure 59. Forest plot of comparison: 1 G-CSF/GM-CSF versus control, outcome: 1.12 Adverse events: thrombosis and related complications (TIA, MI, cerebral non-hemorhagic infarction).



Skin rash and injection site reaction

Two trials including 232 patients reported 33 cases of skin rash in the GM-CSF group and four in the control group (RR 7.69; 95% CI 2.84 to 20.82) (Gerhartz 1993; Aglietta 2000); see Figure 60. There was no significant statistical heterogeneity among the trials (chi squared = 0.90, df = 1, P = 0.34). Data for G-CSF were not reported. Injection site reactions were reported in two trials with 337 patients. Based on 43 observed events in the treatment group and six in the control group, the risk of an injection site reaction was increased more than fivefold (RR 6.55; 95% CI 3.01 to 14.25) (Gerhartz 1993; Gisselbrecht 1997); see Figure 61. There was no significant statistical heterogeneity among the trials (chi squared = 0.00, df = 1, P = 0.97). However, the wide confidence intervals indicate that these results should be interpreted with caution.

Figure 60. Forest plot of comparison: 1 G-CSF/GM-CSF versus control, outcome: 1.13 Adverse events: skin rash.

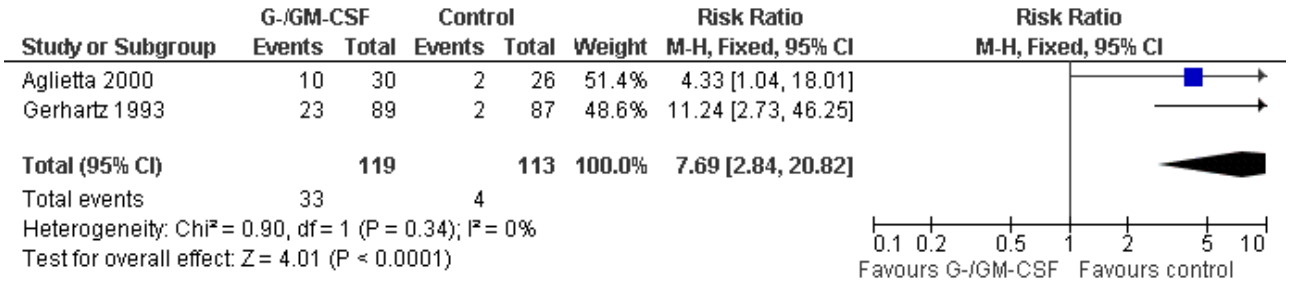
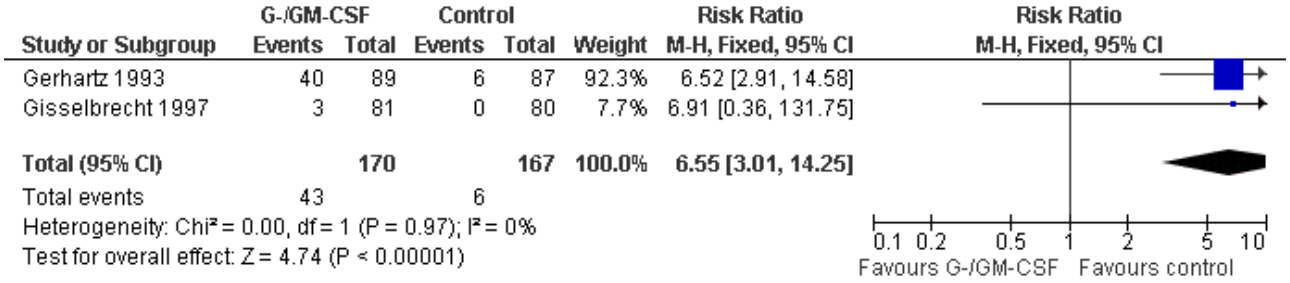


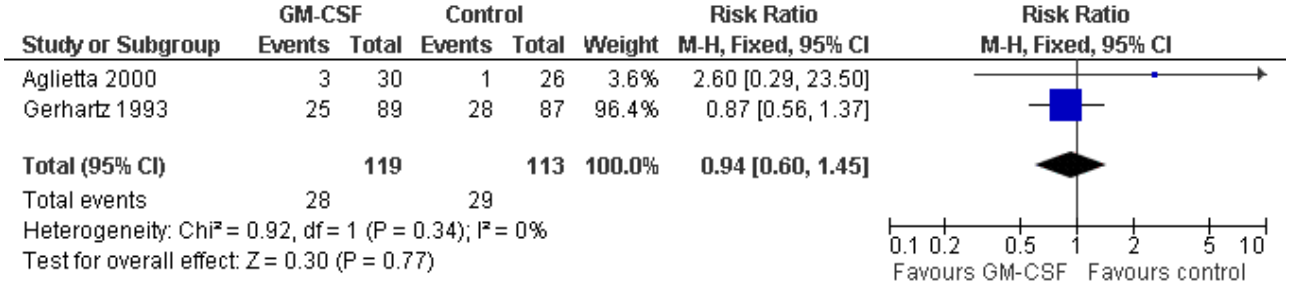
Figure 61. Forest plot of comparison: 1 G-CSF/GM-CSF versus control, outcome: 1.14 Adverse events: injection site reaction.



Myalgia

Two studies including 232 patients failed to detect a significant effect (RR 0.95; 95% CI 0.60 to 1.45) (Gerhartz 1993; Aglietta 2000); see Figure 62. There was no significant statistical heterogeneity among the trials (chi squared = 0.92, df = 1, P = 0.34). No other studies could be analysed for this outcome, so the data must be interpreted cautiously.

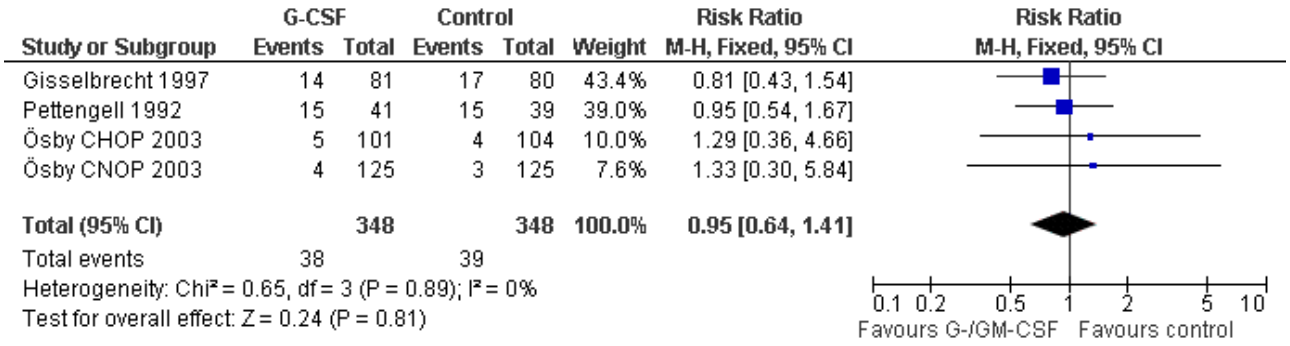
Figure 62. Forest plot of comparison: 1 G-CSF/GM-CSF versus control, outcome: 1.15 Adverse events: myalgia.



Mucositis

Three studies (one examining two chemotherapy regimens) including 696 patients did not show a significant effect (RR 0.95; 95% CI 0.64 to 1.41) (Pettengell 1992; Gisselbrecht 1997; Ösby 2003); see Figure 63. There was no significant heterogeneity among the trials (chi squared = 0.65, df = 3 P = 0.89).

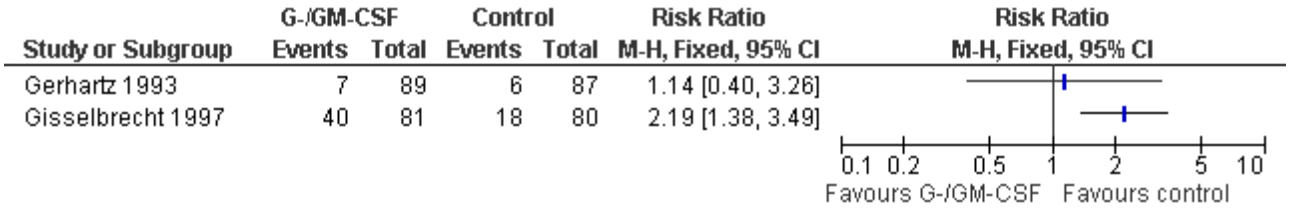
Figure 63. Forest plot of comparison: 1 G-CSF/GM-CSF versus control, outcome: 1.16 Adverse events: mucositis.



Headache

Two studies reported the incidence of headache (Gisselbrecht 1997; Gerhartz 1993); see Figure 64.

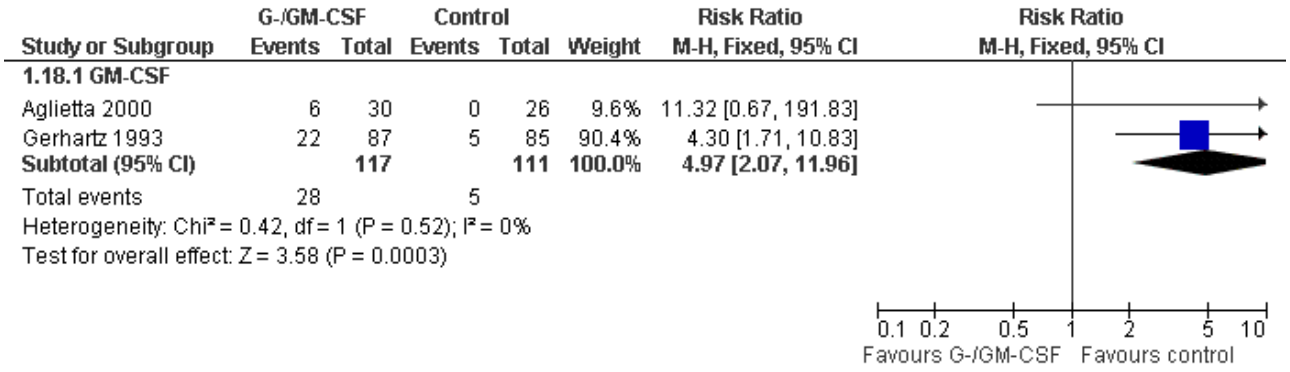
Figure 64. Forest plot of comparison: 1 G-CSF/GM-CSF versus control, outcome: 1.17 Adverse events: headache.



Withdrawal from treatment

Eight studies reported rates of withdrawal from treatment (Pettengell 1992; Gerhartz 1993; Avilés 1994; Fridrik 1997; Gisselbrecht 1997; Dunlop 1998; Aglietta 2000; Doorduijn 2003). Overall, 113 of 531 patients in the G-/GM-CSF group and 122 of 518 patients in the control group withdrew from treatment. In the GM-CSF treated groups, 28 of 117 patients and 5 of 111 patients in the control group left the study due to adverse events attributable to the study medication; see Figure 65. None of the withdrawals in the G-CSF group were related to the study drug.

Figure 65. Forest plot of comparison: 1 G-CSF/GM-CSF versus control, outcome: 1.18 Withdrawals due to adverse events.



The likelihood of experiencing chemotherapy-related adverse events such as nausea, vomiting, peripheral polyneuropathy and alopecia was similar between the G-CSF and GM-CSF treatment groups (Pettengell 1992; Gerhartz 1993; Avilés 1994; Fridrik 1997; Doorduijn 2003; Ösby 2003).

Continuous outcome data

Insufficient reporting of continuous data precluded analysis of the duration of neutropenia and febrile neutropenia, received dose intensity, duration of antibiotic therapy and length of hospital stay.

Duration of neutropenia

Two studies (Gisselbrecht 1997; Aglietta 2000) reported a shortened duration of severe neutropenia (ANC < 500), which was statistically significant in one trial (Gisselbrecht 1997). Other trials reported the duration of neutropenia (ANC <1000) with

inconclusive results. Thus, there is no conclusive evidence that G-CSF or GM-CSF shorten the duration of neutropenia. Refer to Table 2 for an overview of how trials reported the duration of neutropenia and of reported results.

Duration of febrile neutropenia

Two studies reported equal lengths of febrile neutropenia for the two treatment groups (Fridrik 1997; Dunlop MOPP 1998), while two other studies observed a longer duration of febrile neutropenia in the control group (Avilés 1994; Doorduijn 2003). Due to the very limited data available there is no conclusive evidence that G-CSF or GM-CSF reduce the duration of febrile neutropenia (see Table 3).

Hospital stay

Six studies reported data on the duration of hospitalisation. Only one study reported the overall number of days in hospital (Doorduijn 2003). There was no significant difference between the study groups (5 days in the G-CSF group, 6 days in the control group, P = 0.4). Most studies reported effectiveness and efficacy parameters on related measurements, e.g. chemotherapy-related and chemotherapy-unrelated services (Souêtre 1994), hospitalised days per cycle (Dunlop 1998), total number of hospitalised days (Avilés 1994), hospitalised days because of febrile neutropenia (Fridrik 1997) or number of patients hospitalised for more than 3 days for infection (Pettengell 1992). The data reported were too divergent to draw meaningful conclusions (see Table 4).

Duration of parenteral antibiotic treatment

In three studies (Souêtre 1994; Aglietta 2000; Doorduijn 2003) the duration of parenteral antibiotic treatment was shorter in the G-/GM-CSF treated group, but this was not statistically significant. A met-analysis was not performed since the data did not appear to be normally distributed (see Table 5).

Relative Dose Intensity

Relative dose intensity was reported in 9 out of 13 studies. In all but one study (Dunlop MOPP/EVAP 98), the G-CSF or GM-CSF treated group received a higher dose intensity than the control group. In three studies, the overall differences were statistically significant (Pettengell 1992; Fridrik 1997; Gisselbrecht 1997). Other studies found differences for single substances, but the data were not analysed as the required standard deviation was reported in only two studies (Gisselbrecht 1997; Doorduijn 2003) (see Table 6).

Other outcomes

Thrombocytopenia

The rate or the degree of thrombocytopenia was reported in 6 out of 13 trials (Pettengell 1992; Gerhartz 1993; Fridrik 1997; Zinzani 1997; Dunlop 1998; Aglietta 2000). As the available data were measured in different, non-convertible units, it was not possible to conduct a meta-analysis. Overall, Fridrik 1997 showed a significant difference in the mean platelet nadir for thrombocytopenia in favour of the control group. Some studies showed inconsistent and statistically non-significant results in favour of the G-/GM-CSF group (Dunlop MOPP 1998; Aglietta 2000). Others favoured the control group (Gerhartz 1993; Dunlop MOPP/EVAP 98) or reported similar results for both treatment groups (Pettengell 1992; Zinzani 1997). Overall, there is no conclusive evidence that G-CSF or GM-CSF influence the rate or the degree of thrombocytopenia (see Table 7).

Anaemia

The rate or the degree of anaemia was reported in 4 out of 13 trials (Pettengell 1992; Fridrik 1997; Zinzani 1997; Dunlop 1998). As the available data were measured in different, non-convertible units it was not possible to conduct a meta-analysis. Fridrik 1997 showed a statistically significant difference in the haemoglobin level in favour of the control group. The other studies found no significant difference in effect between the two treatment groups. There is no conclusive evidence that G-CSF or GM-CSF influence the incidence or degree of anaemia (see Table 8).

Potential biases

To assess potential biases, previously specified sensitivity and subgroup analysis were performed.

Selection bias

Information on the method of allocation concealment was not available in three studies (Pettengell 1992; Bastion 1993; Burton 2006), but concealment of allocation was adequate in all the other studies. However, inclusion or exclusion of these three studies did not significantly affect any of the outcomes analysed (neutropenia, febrile neutropenia, infection, overall survival, bone pain).

Performance bias

Five of the included studies were placebo-controlled (Bastion 1993; Gerhartz 1993; Avilés 1994; Gisselbrecht 1997; Aglietta 2000). However, sensitivity analysis for placebo-controlled and open label studies did not show significant differences for objective outcome measures, such as neutropenia, febrile neutropenia, infection, tumour response and overall survival, or for subjective outcome measures such as bone pain.

Attrition bias

Seven studies (Cunningham*; Pettengell 1992; Avilés 1994; Gisselbrecht 1997; Aglietta 2000; Doorduijn 2003; Ösby 2003) and one substudy (Dunlop MOPP 1998) were based on an intention-to-treat analysis and included all patients who were initially assigned to treatment in the final analysis. The other studies were based on full set analysis and excluded patients who did not meet the eligibility criteria, had major protocol violation or did not receive any study medication. To assess the influence of the excluded data we performed a worst case-best case scenario analysis. None of the results analysed differed markedly from the pooled data reported. One study reported an additional per protocol analysis of patients who received at least 70% of the study medication (Gerhartz 1993). Inclusion of these data resulted in a significantly reduced risk of parenteral antibiotic treatment in the fixed effect model (RR 0.72; 95% CI 0.54 to 0.97). However, this result was not robust in the random effects model, where more weight is given to smaller studies (RR 0.72; 95% CI 0.42 to 1.22). We excluded these data from the final analysis as we consider per protocol analysis to be less reliable than intention-to-treat.

Publication bias

The funnel plot analysis of the data for complete response and parenteral antibiotic treatment showed an imbalance of positive and negative results, indicating that studies with negative findings might be under-represented. Taking this into consideration, the estimated benefit of G-CSF and GM-CSF in improving complete response and reducing the need for antibiotic treatment may be overestimated.

Reporting bias

Overall, none of the outcomes showed a significant difference between published and unpublished or unreported data.

In addition, subgroup analyses were performed to investigate the influence of clinical diversity of the included trials. Use of antibiotic prophylaxis showed a difference between the analysed subsets only for neutropenia, as mentioned before. Other results such as OS, complete response, febrile neutropenia, infection and bone pain were not influenced. Use of G-CSF or GM-CSF resulted in a significant difference only for the rate of bone pain. Different disease entities (HD and NHL) did not show significant differences in any of the results analysed.

DISCUSSION

The results of this meta-analysis are as follows.

1. There is no evidence that G-CSF and GM-CSF improve overall survival or freedom from treatment failure when used as an adjunct in conventional chemotherapy regimens.
2. Granulopoiesis-stimulating factors (G-CSF and GM-CSF) reduce the risk of neutropenia, febrile neutropenia and infection in patients undergoing conventional chemotherapy for malignant lymphoma.

Our review is the first comprehensive meta-analysis evaluating the effects of G-CSF or GM-CSF in patients with malignant lymphoma undergoing conventional chemotherapy. Other analyses included either studies with smaller numbers of patients or have heterogeneous populations which include solid tumours and haematological malignancies (ASCO Guidelines 1994; ASCO Guidelines 1996; Rusthoven 1998; ASCO Guidelines 2000; Lyman 2002; ASCO Guidelines 2006; Kuderer 2007; Sung 2007). The current, updated review includes thirteen prospectively randomised studies with 2607 patients. In addition, we included previously unreported data on outcome, patient characteristics and study design provided on request by the authors of the original publications. One previously unpublished study was also included. The robustness of all results was tested by sensitivity and subgroup analysis based on prospectively defined parameters.

The most convincing effects of G-CSF and GM-CSF were on neutropenia. G-CSF and GM-CSF reduced the risk of lymphoma patients having neutrophil counts below 0.5 x 10^9/litre by 33%. G-CSF reduced the risk of febrile neutropenia (ANC below 1.0 x 10^9/litre) by 26% and by 41% when ANC was defined as < 0.5 x 10^9/litre. The risk of acquiring infection when given G-CSF or GM-CSF was also reduced by 26%. However, there is no evidence that G-CSF and GM-CSF decrease overall or infection related mortality during chemotherapy.

Data presented in this analysis suggest smaller effects than previously reported (ASCO Guidelines 1994; ASCO Guidelines 1996; Rusthoven 1998; ASCO Guidelines 2000; Hackshaw 2004; ASCO Guidelines 2006; Kuderer 2007). Our results are comparable to the most comprehensive meta-analysis in all cancer patients by Sung 2007, where the subgroup of patients with solid tumours or lymphoma has a relative risk reduction for febrile neutropenia of 36% (RR 0.64; 95% CI 0.53 to 0.76).

Publication bias due to under-reporting of unexpected or negative data is one of the major obstacles in conducting meta-analyses. Comprehensive literature searching and detection of unreported data can minimise this bias. The funnel plot analysis of the data for complete response showed an imbalance of positive and negative results, indicating that studies with negative findings might be under-represented. We identified two studies on GM-CSF that were never published and were not included in this review (Liberati 1991; Unpublished trial). Taking this into consideration, the true effect of G-CSF and GM-CSF on complete response may be even less than indicated by our analysis.

According to Deeks 2001, meta-analysis of continuous outcome data, e.g. duration of neutropenia and number of days in hospital, requires a normal distribution as well as the mean response and the standard deviation. However, most of the included studies did not report these parameters, rendering a meta-analysis impossible. Single studies in malignant lymphoma (Gisselbrecht 1997; Dunlop 1998) and solid tumours (Crawford 1991; Bui 1995; Chevallier 1995; Mayordomo 1995) documented a significantly shorter time to neutrophil recovery in patients treated with G-CSF. In contrast, there is no convincing evidence that G-CSF and GM-CSF decrease the length of febrile neutropenia in patients with both malignant lymphoma (Fridrik 1997; Dunlop 1998) and solid tumours (Crawford 1991; Bui 1995; Chevallier 1995) who are undergoing moderately myelosuppressive chemotherapy.

Apart from reducing infections and related complications, G-CSF and GM-CSF are used in clinical practice to maintain dose intensities. Retrospective analysis indicated that a higher relative dose intensity may translate into better tumour control (DeVita 1987; Lepage 1993). A significantly higher received dose intensity in patients receiving G-/GM-CSF was demonstrated in patients with small cell lung cancer (Trillet-Lenoir 1993; Woll 1995; Fukuoka 1997), breast cancer (de Graaf 1996) and malignant lymphoma (Pettengell 1992; Fridrik 1997; Gisselbrecht 1997; Doorduijn 2003). However, we were unable to quantify the received dose intensity described in the included studies. Most of the G-/GM-CSF treated groups received more chemotherapy compared with the corresponding control groups; four studies demonstrated a statistically significant difference for the main components (Pettengell 1992; Fridrik 1997; Gisselbrecht 1997; Doorduijn 2003).

There was no evidence that the addition of G-CSF or GM-CSF to standard chemotherapy improves tumour response, FFTF or OS in lymphoma patients. The most likely explanation for the very similar complete response rates in patients receiving or not receiving G-/GM-CSF is that the studies focused on the prevention of neutropenia and neutropenia-related events. Studies comparing dose escalated or time intensified chemotherapy regimens with a standard chemotherapy regimen were explicitly excluded from the present analysis.

Adverse effects attributable to G-CSF and GM-CSF, such as bone pain and skin reactions, were more frequently reported in patients treated with G-CSF and GM-CSF than the control group. There was no evidence that thrombosis or related complications occur more frequently in the G-CSF and GM-CSF treated groups than in the control group (odds ratio 1.31; 95% CI 0.54 to 3.19). These findings are consistent with a previous meta-analysis of thrombosis in patients with various malignancies treated with haematopoietic growth factors (odds ratio 1.67; 95% CI 0.92 to 3.04, N = 838) (Barbui 1996). Overall, more patients receiving GM-CSF (24/117) discontinued the study due to adverse effects compared with patients receiving G-CSF. Based on these data, G-CSF seems to be superior to GM-CSF in terms of tolerability. However, it should be taken into consideration that this result is based on an indirect comparison, and that data for G-CSF may simply not have been reported. Similarly, subgroup analysis suggests

that patients receiving G-CSF are more likely to develop bone pain than patients receiving GM-CSF. However, results from single studies, comparing directly G-CSF and GM-CSF, do not support this hypothesis (Beveridge 1998; Alvarado Ibarra 1999).

Although G-CSF and GM-CSF are cost intensive drugs, economic evaluations have demonstrated an overall cost reduction of treatment due to fewer and shorter hospital admissions (Lyman 1995; Lyman 1998). These calculations were based on the assumption that G-CSF would reduce the risk of febrile neutropenia by 50%. However, this figure relates to a randomised controlled study including 211 patients with small cell lung cancer (Crawford 1991). In our updated analysis, the relative risk reduction for febrile neutropenia with ANC below 1.0 x 109 per litre was 26% and for ANC below 0.5 x 109 per litre 41% in lymphoma patients. A threshold risk for febrile neutropenia in a given cancer population of 40% was estimated at which the added costs of G-CSF would be counterbalanced by the reduced direct hospital costs for febrile neutropenia (Lyman 1995). An updated analysis added the indirect institutional costs of care for patients with febrile neutropenia to the direct costs, reducing the potential break-even point to a febrile neutropenia risk of 20% (Lyman 1998). In addition, this threshold was swon to be effective in breast cancer patients receiving chemotherapy (Vogel 2005) and it now recommended in current guidelines (EORTC Guidelines 2006; ASCO Guidelines 2006).

In addition to the prevention of neutropenia and related effects, growth factors are currently used in high dose chemotherapy settings to help generate haematopoietic stem cells and to support recovery after myeloablative treatment (de Witte 1992; Pettengell 1993). More recently, growth factors have been used to not only facilitate not only the administration of the planned chemotherapy in dose and time but also to assist haematopoietic recovery in time- or dose-intensified regimen. There are strong arguments for this notion stemming from three large prospectively randomised trials in patients with HD (Diehl 2003) and NHL Preundschuh 2004a; Preundschuh 2004b). Thus, a further meta-analysis to prove the assumed role of haematopoietic growth factors in dose escalation is warranted.

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence that G-CSF or GM-CSF improve OS or FFTF. We demonstrated that G-CSF and GM-CSF significantly reduce the risk for neutropenia, febrile neutropenia and infections in patients undergoing conventional chemotherapy for malignant lymphoma. .

Implications for research

Clinical studies and meta-analyses to prove the effectiveness of growth factors in assisting haematopoietic recovery in time- or dose-intensified regimen are warranted.

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CHARACTERISTICS OF STUDIES

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

Aglietta 2000

Methods	RCT, 1991-94, allocation concealed*
Participants	56 patients randomised, age 18-77, gender m/f: 33/23, country: Italy Hodgkin's disease, biopsy proven*, untreated, stage II-IV
Interventions	1. CT Mechlorethamine 6 mg/m^2, iv, d1

Aglietta 2000 *(Continued)*

	Vincristine 1.4 mg/m^2, max 2.0 mg/m^2, iv, d1 Procarbazine 100 mg/m^2, po, d1-7 Prednisone 40 mg/m^2, po, d1-7 Doxorubicin 25 mg/m^2, iv, d15 Bleomycin 10 mg/m^2, iv, d15 Vinblastine 6 mg/m^2, iv, d15 Dacarbazine 375 mg/m^2, iv, d15 this regimen was repeated every 28 days times 6 2. GM-CSF (5 µg /kg/day s.c. prior to each chemotherapy cycle), used d7-4 before first cycle, d8-11 and d22-25 each subsequent cycle 3. no placebo given 4. no AB prophylaxis given*
Outcomes	primary endpoints: adherence to the planned delivery rate of planned CT secondary endpoints: nadir neutrophil counts, total duration of neutropenia, total number of days of antibiotic or antifungal treatment, additional outcomes: adverse effects, tumour response
Notes	funding: Italian Association for Cancer Research and Novartis Farma, S.p.A., Italy

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Aglietta 2000*

Methods	Additional information obtained by personal communication with the study author.
Participants	see Aglietta 2000
Interventions	see Aglietta 2000
Outcomes	see Aglietta 2000
Notes	see Aglietta 2000

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Avilés 1994

Methods	RCT, 3/1992-9/1992*, computer generated numbers, allocation concealed
Participants	42 patients randomised age: 34-63*, mean age 51 gender: m/f: 18/24 country: Mexico NHL diffuse large cell lymphoma, intermediate and high grade, untreated; stage: IV*
Interventions	1. alternating ESAP, m-BECOD, MVPP-Bleo by 9 cycles details of CT: Etoposide 40 mg/m^2, iv, d1-4 Methylprednisolone 350 mg/m^2, iv, d1-5 Ara-C 2 g/m^2, iv, d5 Cis-Platin 25 mg/m^2, iv, d1-4 Bleomycin 10 mg/m^2, iv, d1 Epirubicin 70 mg/m^2, iv, d1 Cyclophosphamide 600 mg/m^2, iv, d1 Vincristine 1.4 mg/m^2, iv, d1 Dexamethasone 20 mg/m^2, po, d1-5 Methotrexate 120 mg/m^2, iv, d14 Mitoxantrone 10 mg/m^2, iv, d1 Vincristine 1.4 mg/m^2, iv, d1 Prednisone 50 mg/m^2, iv, d1-14 Procarbazine 100 mg/m^2, po, d1-14 2. G-CSF (5 µg/kg/day, sc, d6-15) 3. placebo given* 4. no AB prophylaxis
Outcomes	duration of leucopenia and granulocytopenia, frequency and severity of infections, hospitalisation, deaths, tumour response, dose intensity, treatment delay, antibiotic use
Notes	funding: Roche Mexcio*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Avilés 1994*

Methods	additional information obtained by personal communication with the study author
Participants	see Avilés 1994
Interventions	see Avilés 1994
Outcomes	see Avilés 1994
Notes	see Avilés 1994

Risk of bias

Avilés 1994* *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Bastion 1993

Methods	RCT, 1990-1992, allocation unclear
Participants	119 patients no details available
Interventions	1. CT A: 3-4 courses ACVBP, 21 days B: 2 ACVBP alternat. 2x VIMMM, 21 days ACVBP: Adriamycin 75 mg/m^2, d1 Cyclophsophamide 1200 mg/m^2, d1 Vindesine 2 mg/m^2, d1 and 5 Bleomycin 10 mg, d1 and 5 Prednisolone 60 mg/m^2, d1-5 Methotrexate 12 mg intrathecal 1-2 /week VIMMM: VP 16 100 mg/m^2, d1 and 5 Ifosfamide 1000 mg/m^2, d1-5 Mitoxantrone 10 mg/m^2, d1 Methyl GAG 300 mg/m^2, d1 and 5 Methotrexate 1500 mg/m^2, d15 Methylprednison 60 mg/m^2, d1-5 2. G-CSF: 5 µg/kg/day, sc, d6-max d19) 3. placebo given 4. no AB prophylaxis
Outcomes	risk of febrile neutropenia and documented infection, duration of neutropenia, mortality during induction, dose-intensity
Notes	funding: Amgen

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Bastion ACVBP 1993

Methods	see Bastion 1993, arm A
Participants	see Bastion 1993, arm A
Interventions	see Bastion 1993, arm A

Bastion ACVBP 1993 *(Continued)*

Outcomes	see Bastion 1993, arm A
Notes	see Bastion 1993, arm A

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Bastion VIMMM 1993

Methods	see Bastion 1993, arm B
Participants	see Bastion 1993, arm B
Interventions	see Bastion 1993, arm B
Outcomes	see Bastion 1993, arm B
Notes	see Bastion 1993, arm B

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Björkholm 1999

Methods	This is the abstract publication to Ösby 2003. Apart from G-CSF randomisation this study included 2 different treatment arms. See Björkholm CHOP 1999 and Björkholm CNOP 1999.
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Björkholm CHOP 1999

Methods	RCT, 1992-97, concealed allocation

Björkholm CHOP 1999 *(Continued)*

Participants	205 patients randomised, age >60 stage II-IV high-grade NHL, untreated
Interventions	CHOP with G-CSF versus CHOP without G-CSF 1. CT: Cyclophosphamide 750 mg/m^2, iv, d1 Vincristine 1.4 mg/m^2, iv, d1 Doxorubicin 50 mg/m^2, iv, d1 Prednisone 100 mg/m^2, po, d1-5 2. G-CSF (5 µg/kg/day, sc, d2-d10/14) 3. no placebo given* 4. no AB prophylaxis given*
Outcomes	toxicity (severe neutropenia, infections), tumour response, survival
Notes	funding: Roche, Amgen, Wyeth Lederle and the Swedish Cancer Society

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Björkholm CNOP 1999

Methods	RCT, 1992-97, concealed allocation
Participants	250 patients randomised, age >60 stage II-IV high-grade NHL, untreated
Interventions	CNOP with G-CSF versus CNOP without G-CSF 1. CT: Cyclophosphamide 750 mg/m^2, iv, d1 Mitoxantrone 10 mg/m^2, iv, d1 Vincristine 1.4 mg/m^2, iv, d1 Prednisone 100 mg/m^2, po, d1-5 2. G-CSF (5 µg/kg/day, sc, d2-d10/14) 3. no placebo given* 4. no AB prophylaxis given*
Outcomes	toxicity (severe neutropenia, infections), tumour response, survival
Notes	funding: Roche, Amgen, Wyeth Lederle and the Swedish Cancer Society

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Burton 2006

Methods	Apart from the G-CSF randomisation, the trial also randomised to CHOp or PMitCEBO see Burton CHOP and Burton PMitCEBO. Overall survival reported only for the full group. RCT, 1997-2003, allocation concealment unclear
Participants	784 patients randomised, previously untreated, age >= 60 years Stage Ia bulky or Ib to IV aggressive NHL (diffuse mixed cell, diffuse large cell, diffuse immunoblastic and after 2000 diffuse large B-cell lymphoma)
Interventions	CHOP or PMitCEBO
Outcomes	Overall survival, on treatment mortality, infection related mortality, overall response rate, toxicity (but not for G-CSF vs. control except for the incidence of neutropenia)
Notes	public funding acknowledged

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	No information provided

Burton CHOP 2006

Methods	RCT, 1997-2003, allocation concealment not reported
Participants	784 patients randomised, previously untreated, age >= 60 years 397 randomised to PMitCEBO Stage Ia bulky or Ib to IV aggressive NHL (diffuse mixed cell, diffuse large cell, diffuse immunoblastic and after 2000 diffuse large B-cell lymphoma)
Interventions	1. CT: Cyclophosphamide 300mg/m^2 d1 Mitoxantrone 7mg/m^2 d1 Etopside 150mg/m^2 d1 Prednisolone 50mg daily week 1-4, 50mg alternating days weeks 5 to treatment end Vincristine 1.4 mg/m^2 d8 Bleomycin 10mg/m^2 d8 2. G-CSF: 263µg/day lenograstim d 6-12 3. no placebo given 4. cotrimoxazole given week one to treatment end plus two weeks
Outcomes	On treatment mortality, infection related mortality, overall response rate, toxicity (but not for G-CSF vs. control except for the incidence of neutropenia)
Notes	Subgroup of Burton 2006, with patients randomised to treatment with PMitCEBO

Burton PMitCEBO 2006

Methods	RCT, 1997-2003, allocation concealment not reported
Participants	784 patients randomised, previously untreated, age >= 60 years 397 randomised to PMitCEBO Stage Ia bulky or Ib to IV aggressive NHL (diffuse mixed cell, diffuse large cell, diffuse immunoblastic and after 2000 diffuse large B-cell lymphoma)
Interventions	1. CT: Cyclophosphamide 750mg/m^2 d1 Doxorubicin 50mg/m^2 d1 Vincristine 1.4 mg/m^2 d8 Prednisolone 100mg d1-5 2. G-CSF: 263µg/day lenograstim d 8-14 3. no placebo given 4. cotrimoxazole given week one to treatment end plus two weeks
Outcomes	On treatment mortality, infection related mortality, overall response rate, toxicity (but not for G-CSF vs. control except for the incidence of neutropenia)
Notes	Subgroup of Burton 2006 with patients randomised to CHOP

Cunningham*

Methods	RCT, 1993-1995*, concealed allocation*
Participants	39 patients randomised, age 23-68, gender m/f: 22/17 country: UK relapsed NHL (N = 38) relapsed HD (N = 1) stage I-IV, biopsy proven
Interventions	ECP +/- G-CSF 1. CT Etoposide 50 mg/m^2, po, d1-10 Cisplatin 60 mg/m^2, iv, d1 Prednisolone 100 mg, po, d1-5 2. G-CSF 5 µg/kg/day, sc, d11-17 3. no placebo given* 4. AB prophylaxis given
Outcomes	toxicity, response rate, duration of response, survival
Notes	funding: ?? This study was never published. All data presented in this review were kindly provided by Dr. Cunningham.

Cunningham* *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Doorduijn 2003

Methods	RCT, 1994-2000, concealed allocation*
Participants	389 patients randomised, age 65-90, median 72, gender m/f: 216/173 country: Netherlands, Belgium stage II-IV high-grade NHL, untreated
Interventions	CHOP with G-CSF versus CHOP without G-CSF 1. CT: Cyclophosphamide 750 mg/m^2, iv, d1 Doxorubicin 50 mg/m^2, iv, d1 Vincristine 1.4 mg/m^2, iv, d1 Prednisone 50 mg/m^2, po, d1-5 2. G-CSF 300 µg/day sc, d2-d11 3. no placebo given 4. no AB prophylaxis given
Outcomes	received dose intensity, severe neutropenia and infections, tumour response, survival, QoL, costs
Notes	supported by the Dutch National Health Council

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Dunlop 1998

Methods	Apart from G-CSF randomisation this study included 2 different treatment arms. See Dunlop MOPP 1998 and Dunlop MOPP/EVAP 98.
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Dunlop MOPP 1998

Methods	RCT, 1/1991-6/1993*, allocation by phoning central AMGEN Data Centre
Participants	25 patients randomised and evaluated, age 19-41, gender m/f: 15/10, country: UK Hodgkin's disease, biopsy proven*, untreated, stage IB-IV
Interventions	1. CT Mustine 6 mg/m^2, iv, d1and 8 Vincristine 1.4 mg/m^2, iv, d1 and 8 Procarbazine 100 mg/m^2, po, d1-14 Prednisolone 25 mg/m^2, po, d1-14 2. G-CSF (rmetHuG-CSF [Amgen] 5 microgram/kg/d sc d15-d28 of each cycle) 3. no placebo used 4. no prophylactic antibiosis allowed.
Outcomes	dose intensity, toxicity (duration and nadir leucopenia, febrile neutropenia, incidence, grade and duration of infections), hospitalisation
Notes	funding: Amgen, Thousand Oaks, CA

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Dunlop MOPP 1998*

Methods	Additional information obtained by personal communication with the study author.
Participants	see Dunlop MOPP 1998
Interventions	see Dunlop MOPP 1998
Outcomes	see Dunlop MOPP 1998
Notes	see Dunlop MOPP 1998

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Dunlop MOPP/EVAP 98

Methods	RCT, 1/1991-6/1993*, allocation by phoning central AMGEN Data Centre
Participants	28 patients randomised, 22 evaluated, age 19-41, gender m/f: 15/7, country: UK, Hodgkin's disease,biopsy proven*, untreated, stage IB-IV Hodgkin's disease
Interventions	1. CT

Dunlop MOPP/EVAP 98 *(Continued)*

	Mustine 6 mg/m^2, iv, d1and 8 Vincristine 1.4 mg/m^2, iv, d1 Procarbazine 100 mg/m^2, po, d1-7 Prednisolone 25 mg/m^2, po, d1-14 Etoposide 75 mg/m^2, iv, d8-10 Adriamycin 25 mg/m^2, iv, d8 Vinblastine 6mg/m^2, iv, d8 2. G-CSF (5 microgram/kg/d sc d11-d28 of each cycle rmetHuG-CSF by Amgen) 3. no placebo used 4. no prophylactic antibiosis allowed
Outcomes	dose intensity, toxicity (duration and nadir leucopenia, febrile neutropenia, incidence, grade and duration of infections), hospitalisation
Notes	funding: Amgen, Thousand Oaks, CA

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Dunlop MOPP/EVAP 98*

Methods	Additional information obtained by personal communication with the study author.
Participants	see Dunlop MOPP/EVAP 98
Interventions	see Dunlop MOPP/EVAP 98
Outcomes	see Dunlop MOPP/EVAP 98
Notes	see Dunlop MOPP/EVAP 98

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Engelhard 1994

Methods	see Gerhartz 1993c
Participants	see Gerhartz 1993c
Interventions	see Gerhartz 1993c
Outcomes	probability of survival, duration of CR
Notes	see Gerhartz 1993

Risk of bias

Engelhard 1994 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Fridrik 1997

Methods	RCT, 1991-95, central allocation*
Participants	85 patients randomised, 74 pts evaluated, age: 19-72*, median age 52, gender m/f: 43/31, country: Austria, high grade NHL, untreated, stage I-IV
Interventions	1. CT Cyclophosphamide 750 mg/m^2, iv, d1 Epirubicin 70 mg/m^2, iv, d1 Vincristine 1.4 mg/m^2, iv, d1 and 8 Prednisolone 100 mg po, d1-5 Ifosfamide 2000 mg/m2, iv, d15-17 Uromitexane 400 mg/m^2, iv, d15-17 VP16 100 mg/m^2, iv, d15-17 Dexamethasone 40 mg/m^2, po, d15-19 Methotrexate 800 mg/m^2, iv, d22 Ca-folinate 15 mg/m^2, po, d23-25 2. G-CSF (E.coli derived, Amgen) was given in a dose of 5 µg/kg on d2-7, d9-14, d18-21 and d23-27. After 10 G-CSF receiving patients entered the study, the dose was modulated, and instead of d9-14 G-CSF was given 2 days less, thus d9-12 3. no placebo used 4. no AB prophylaxis given*
Outcomes	incidence of febrile neutropenia, febrile episodes, number of documented infections, use of iv antibiotics, number of days in hospital due to febrile neutropenia, dose intensity, tumour response, time to first febrile neutropenia, time to relapse, time to treatment failure, survival, adverse effects
Notes	funding: Roche Austria, later AMGEN*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Fridrik 1997*

Methods	Additional information obtained by personal communication with the study author.
Participants	see Fridrik 1997
Interventions	see Fridrik 1997
Outcomes	see Fridrik 1997
Notes	see Fridrik 1997

Risk of bias

Fridrik 1997* *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Gerhartz 1993

Methods	RCT, 1989-91, allocation with central and independent centre, dispatched with numbered study drugs and sealed envelopes
Participants	182 patients randomised, 125 pts analysed for efficacy, 176 pts evaluated for safety analysis, age 15-73, gender m/f: 90/61 country: D high-grade NHL, untreated, stage II-IV, biopsy proven
Interventions	1. CT: Cyclophosphamide 700 mg/m^2, iv, d1 Doxorubicin 60mg/ m^2 , iv, d1 Bleomycin 15 mg absolute dose, iv, d15 Vincristine 1mg/m^2 , iv, d1 and 15 Procarbazine 100 mg/m^2, po, d1-7 Prednisolone 50 mg/m^2 po, d1-7 Mesna 400 mg, iv after cyclophosphamide 2. GM-CSF (unglykosylated GM-CSF produced by Sandoz) 400 µg per patient sc 3. placebo given
Outcomes	leucocyte counts, frequency and severity of infections, tumour response, hospitalisation, freedom from treatment failure, adverse effects
Notes	funding: Sandoz Pharma Ltd

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Gerhartz 1994a

Methods	Follow-up report of Gerhartz 1993 and Engelhard 1994.
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Gisselbrecht 1997

Methods	RCT, 1990-92, concealed allocation*
Participants	162 patients randomised and analysed, age15-55, gender m/f: 15-55, country: F, B intermediate and high grade NHL, histological subtypes: diffuse large cell lymphoma (48%, diffuse mixed lymphoma 17%), stage I-IV, untreated
Interventions	1. CT Cyclophosphamide 1200 mg/m^2, iv, d1 Vindesine 2 mg/m^2, iv, d1 and d5 Bleomycin 10 mg, iv, d1 and d5 Prednisone 60 mg/m^2, po, d1-5 Methotrexate 15 mg intrathecal, d1 Adriamycin 75 mg/m^2, iv, d1 or Mitoxantrone 12 mg/m^2, iv, d1 2. G-CSF (glycosylated recombinant human granulocyte colony-stimulating factor, Chugai) 5 µg/kg/d sc, d6-d13, outpatients 3. placebo 4. no AB prophylaxis given
Outcomes	incidence of fever, infection, neutropenia, adverse effects, dose intensity, tumour response, survival
Notes	funding: Chugai*

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

Gisselbrecht 1997*

Methods	Additional information obtained by personal communication with the study author.
Participants	see Gisselbrecht 1997
Interventions	see Gisselbrecht 1997
Outcomes	see Gisselbrecht 1997
Notes	see Gisselbrecht 1997

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

Pettengell 1992

Methods	RCT, 1989-91, method of allocation not specified

Pettengell 1992 *(Continued)*

Participants	80 patients randomised, age 16-71, gender m/f: 53/27, c: UK, high grade de novo NHL, stage I-IV, histology: diffuse large and mixed cell lymphoma
Interventions	1. CT Adriamycin 35 mg/m^2, iv, d1, 15, 29, 43, 57, 71 Cyclophosphamide 350 mg/m^2, iv, d1, 29, 57 Vincristine 1.4 mg/m^2, iv, d8, 22, 36, 50, 64 Bleomycin 10 mg/m^2, iv, d8, 36, 64 Etoposide 100 mg/m^2, po, d15-19, d43-47, d71-75 Prednisolone 50 mg po, daily for 5 weeks than reduced. 2. G-CSF: rmetHuG-CSF 230 µg/m^2/d, sc, for 13 weeks except days preceeding and during doxorubicin, cyclophosphamide, etoposide 3. no placebo given 4. Antibiotic prophylaxis: cotrimoxazole 960 mg po twice daily and Ketoconazole 200 mg po twice daily both drugs given for 12 weeks with start of CT
Outcomes	tumour response, dose intensity, CT delays, incidence of neutropenia, febrile neutropenia, infections, antibiotic use, hospitalisation, adverse events, overall survival, disease free survival
Notes	funding: supported by Amgen-Roche, the Cancer Research Campaign, Leukaemia Research Fund

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Souêtre 1994

Methods	Economic evaluation of the clinical study published by Gisselbrecht 1997.
Participants	see Gisselbrecht 1997
Interventions	see Gisselbrecht 1997
Outcomes	economic evaluation
Notes	see Gisselbrecht 1997

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Zinzani 1997

Methods	RCT, 1993-95, allocation concealed*
Participants	158 patients randomised, 149 patients evaluated, age 60-82, gender m/f: 69: 80, country: Italy high-grade de novo NHL, stage II-IV, histology: diffuse large-cell centroblastic and immunoblastic lymphoma. anaplastic large cell and peripheral T-cell lymphoma

Zinzani 1997 *(Continued)*

Interventions	1. CT: Cyclophosphamide 300 mg/m^2, iv, d1,15, 29, 43 Mitoxantrone 10 mg/m^2, iv, d1,15,29,43 Vincristine 2 mg, iv, d8, 22, 36, 50 Etoposide 150 mg/m^2, iv, d8 and d36 Bleomycin 10 mg/m^2, iv, d22 and d50 Prednisone 40 mg im, daily, dose tapered over the last 2 weeks 2. G-CSF 3. no placebo 4. AB prophylaxis given
Outcomes	incidence of neutropenia, anaemia, thrombocytopenia and infections; adverse effects, dose intensity, tumour response, relapse free and progression free survival, overall survival
Notes	funding: not pharmaceutically sponsored*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Zinzani 1997*

Methods	Additional information obtained by personal communication with the study author.
Participants	see Zinzani 1997
Interventions	see Zinzani 1997
Outcomes	see Zinzani 1997
Notes	see Zinzani 1997

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Zinzani 1999

Methods	Follow-up report to Zinzani 1997.
Participants	
Interventions	
Outcomes	
Notes	

Zinzani 1999 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Ösby 2003

Methods	this is the full text publication to Björkholm 1999. For details see Björkholm 1999
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Ösby CHOP 2003

Methods	see Björkholm CHOP 1999
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Ösby CNOP 2003

Methods	see Björkholm CNOP 1999
Participants	
Interventions	

Ösby CNOP 2003 *(Continued)*

Outcomes		
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	D - Not used

* data obtained by personal communication with the study author

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

Study	Reason for exclusion
Adde 1998	Follow up report of Magrath 1996.
Anaissie 1996	RCT in the treatment of febrile neutropenia
Bergmann 1995	Patients (N = 35) were randomised to receive either rhGM-CSF or placebo during the first two chemotherapy cycles and rhGM-CSF for all following cycles.
Bertini 1996	Non randomised trial with 67 patients. G-CSF was given according to the drug availability at the specific hospital: "As this factor was not generally available in Italy at that time, only some of the participating centers included it in the treatment program. However, all patients in a single center received the same treatment either with or without G-CSF."
Bodey 1994	RCT in the treatment of febrile neutropenia
Gerhartz 1993ex	Treatment study, 60 pts with established neutropenia were included in this study to receive GM-CSF or placebo at random.
Gianni 1990	Non randomised study (N = 36), NHL and breast cancer patients included, less than 10 NHL pts per study arm.
Gordon 1999	Phase II study without control group.
Gregory 1998	Less than 10 lymphoma pts per study arm.
Gustavsson 1997	Non randomised study with historical control group.
Hansen 1995	Fourteen pts with NHL were randomised to receive G-CSF or no treatment prior to chemotherapy.
Hartmann 1997	randomised intervention study in pts (N = 71) with established neutropenia.
Ho 1990	Non randomised study.
Hovgaard 1992	Dose finding study.
Kaku 1993	Secondary prophylaxis, only pts (N = 62) with granulocytopenia (<1x10^3/µl) after the first cycle of chemotherapy were enrolled.
Kaneko 1991	G-CSF or placebo was started subcutaneously 72 hours after completion of the second cycle of chemotherapy and continued for 14 days. See also Ogawa 1990.

Study	Reason for exclusion
Kaplan 1991	Effect of GM-CSF in patients (N = 21) receiving chemotherapy for human immunodeficiency virus-associated non-Hodgkin's lymphoma, randomised study.
Karthaus 1998	Randomised controlled trial on topical oral G-CSF to prevent mucositis in pts (N = 8) with high-grade lymphoma.
Liberati 1991	Part of a multicenter study. This publication reports on 14 pts with non-Hogkin lymphoma receiving GM-CSF or placebo during chemotherapy. This report was written before the randomised code was made known. The author was contacted. However, we were not able to obtain additional data or information.
Lopez-Hernandez 2000	RCT in the treatment of febrile neutropenia
Magrath 1996	Ths trial analysed a mixed population of children (N = 33) and adults (N = 39). 16 adult lymphoma pts were randomised to receive or not receive GM-CSF. See also Adde 1998.
Maher 1994	RCT in the treatment of febrile neutropenia
Maiche 1993	Secondary prophylaxis: 59 pts who had earlier developed an infection following antineoplastic chemotherapy were randomised to receive either granulocyte colony-stimulating factor (G-CSF) alone or G-CSF + quinolone as prophylaxis during subsequent identical chemotherapy courses.
Mangiagalli 1995	Non randomised study with historical control group. 15 NHL pts received G-CSF, 5 NHL pts served as historical control.
Mayordomo 1995	Treatment study.
Moreau 1997	This trial randomised controlled trial was conducted in pts (N =102) with multiple myeloma.
Motoyoshi 1986	randomised crossover study comparing the hematopoietic effect of partially purified human urinary colony-stimulating factor in 24 pts with malignant lymphoma, solid tumours, or multiple myeloma.
Niitsu 1995	Non randomised study (N = 64).
Ogawa 1990	Japanese publication. Pts with malignant lymphoma were randomised to receive G-CSF or placebo starting 72 hours after the termination of the second cycle of chemotherapy and continued for 14 days. This report seems to be a detailed version of the phase III study that was reported in English by Kaneko 1991.
Rao 2005	randomised controlled trial: 34 patients with CLL (N = 16) or low grade NHL (N = 18), i.e. less than 10 lymphoma patients per arm.
Riccardi 1993	Non randomised trial: 17 consecutive pts with HD received chemotherapy with (N =9) or without (N =8) GM-CSF.
Seymour 1995	randomised controlled dose finding study in pts with solid tumours (N = 55) and malignant lymphoma (N =11).
Shi 1994	Chinese publication, randomised cross over study in 21 pts receiving chemotherapy. Unclear whether lymphoma pts were enrolled. This might be the same study as Shi 1996, however could not be clarified due to lack of language skills.
Shi 1996	randomised cross-over clinical trial in pts with NHL (N = 10) and solid tumours. Language: Chinese. Might be the same study as Shi 1994.

Study	Reason for exclusion
Togawa 2000	Randomised controlled trial of pts (N = 98) with multiple myeloma treated with G-CSF for chemotherapy induced neutropenia. Chugai Ltd. kindly provided us with a translation of the Japanese report.
Unpublished trial	This trial was identified via internet databases. In this multicenter study 100 patients were randomised to receive GM-CSF or placebo during chemotherapy. None of the participating physicians contacted had data of this trial. The pharmaceutical company supposed to be in charge of did not provide information about this study.
Vellenga 1996	RCT in the treatment of febrile neutropenia
Wilson 1998	Non randomised study: the first 16 pts received no G-CSF and the subsequent 29 pts received G-CSF on all cycles.
Yau 1996	Randomised controlled study in pts with breast cancer (N = 46) and malignant lymphoma (N =10).
Yoshida 1999	RCT in the treatment of febrile neutropenia
Zagonel 1994	Non randomised study: 12 consecutive pts received G-CSF during chemotherapy compared to 11 consecutive pts who received the same chemotherapy regimen without growth factor support.

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

Blay

Trial name or title	Elypse 2
Methods	
Participants	patients with malignant lymphoma, all sub-entities included less acute leukemias adult patients (>16 years) undergoing chemotherapy without stem cell transplantation. It is planned to enrol 144 patients.
Interventions	G-CSF or GM-CSF
Outcomes	
Starting date	
Contact information	
Notes	study is still ongoing

Cunningham

Trial name or title	A Phase III Trial comparing CHOP to PMitCEBO with or without G-CSF in patients aged 60 plus with aggressive NHL
Methods	
Participants	elderly patients with aggressive non-Hodgkin's lymphoma, target: N = 410

Cunningham *(Continued)*

Interventions	Two different types of chemotherapy with or without G-CSF
Outcomes	Primary endpoint: comparison of failure-free survival between the groups randomised to PMitCE-BO and CHOP Secondary endpoints: OS, disease specific survival, relapse free survival, death due to toxicity, in-patient days, in-patients days due to sepsis, dose intensity, response rate, toxicity
Starting date	11 March 1997
Contact information	
Notes	study is still ongoing

DATA AND ANALYSES

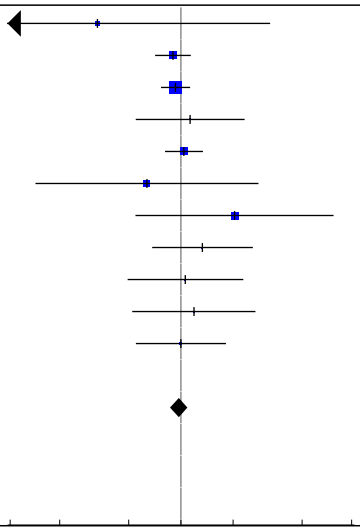
Comparison 1. G-CSF/GM-CSF versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	11	2221	Peto Odds Ratio (95% CI)	0.97 [0.87, 1.09]
2 Freedom from treatment failure	6	718	Peto Odds Ratio (95% CI)	1.11 [0.91, 1.35]
3 Neutropenia	8	1013	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.60, 0.73]
4 Febrile Neutropenia, ANC < 1000	5	360	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.62, 0.89]
5 Febrile Neutropenia, ANC < 500	3	604	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.48, 0.72]
6 Infection	11	1292	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.64, 0.85]
7 Parenteral antibiotic treatment	4	359	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.57, 1.18]
8 Overall mortality during chemotherapy	11	1170	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.60, 1.43]
9 Infection related mortality during chemotherapy	12	1835	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.51, 1.71]
10 Complete response	13	2368	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.95, 1.10]
11 Adverse events: bone pain	9	1204	Risk Ratio (M-H, Fixed, 95% CI)	3.57 [2.09, 6.12]
12 Adverse events: thrombosis and related complications (TIA, MI, cerebral non-hemorhagic infarction)	5	425	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.56, 3.01]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
13 Adverse events: skin rash	2	232	Risk Ratio (M-H, Fixed, 95% CI)	7.69 [2.84, 20.82]
14 Adverse events: injection site reaction	2	337	Risk Ratio (M-H, Fixed, 95% CI)	6.55 [3.01, 14.25]
15 Adverse events: myalgia	2	232	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.60, 1.45]
16 Adverse events: mucositis	4	696	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.64, 1.41]
17 Adverse events: headache	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
18 Withdrawals due to adverse events	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
18.1 GM-CSF	2	228	Risk Ratio (M-H, Fixed, 95% CI)	4.97 [2.07, 11.96]

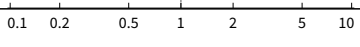
Analysis 1.1. Comparison 1 G-CSF/GM-CSF versus control, Outcome 1 Overall survival.

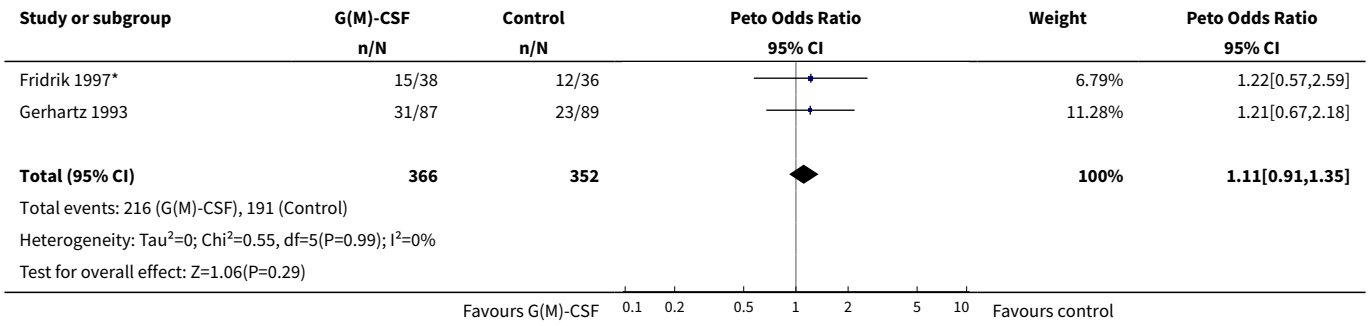
Study or subgroup	G-/GM-CSF n/N	Control n/N	Peto Odds Ratio 95% CI	Weight	Peto Odds Ratio 95% CI
Aglietta 2000*	1/17	2/12		0.26%	0.33[0.03,3.27]
Björkholm 1999	141/226	150/229		24.62%	0.9[0.71,1.14]
Burton 2006	200/387	219/397		37.62%	0.93[0.77,1.13]
Cunningham*	14/18	16/21		2.64%	1.13[0.55,2.33]
Doorduijn 2003	123/197	123/192		22.09%	1.04[0.81,1.34]
Dunlop MOPP 1998*	3/13	4/12		0.63%	0.64[0.14,2.8]
Dunlop MOPP/EVAP 98*	6/14	3/11		0.8%	2.04[0.55,7.59]
Engelhard 1994	22/87	15/85		3.09%	1.33[0.68,2.6]
Fridrik 1997*	14/38	12/36		2.34%	1.06[0.49,2.29]
Pettengell 1992	11/41	12/39		2.07%	1.19[0.52,2.69]
Zinzani 1997	22/77	21/72		3.84%	1[0.55,1.82]
Total (95% CI)	**1115**	**1106**		**100%**	**0.97[0.87,1.09]**
Total events: 557 (G-/GM-CSF), 577 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.59, df=10(P=0.92); I^2=0%					
Test for overall effect: Z=0.46(P=0.65)					



Analysis 1.2. Comparison 1 G-CSF/GM-CSF versus control, Outcome 2 Freedom from treatment failure.

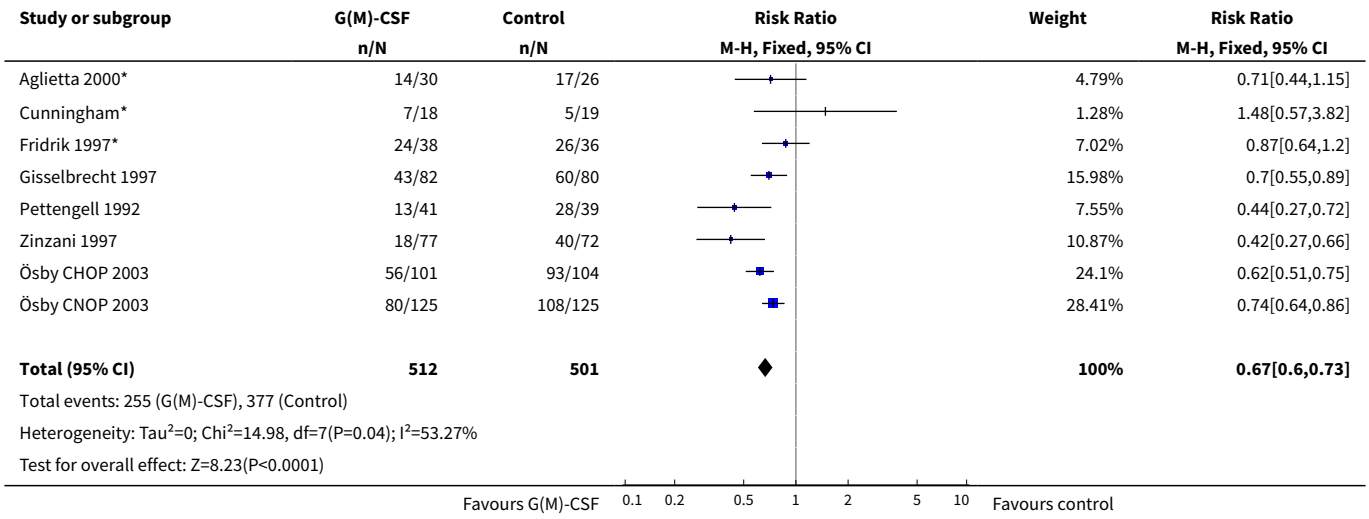
Study or subgroup	G(M)-CSF n/N	Control n/N	Peto Odds Ratio 95% CI	Weight	Peto Odds Ratio 95% CI
Aglietta 2000*	6/17	3/12		2.19%	1.4[0.37,5.27]
Doorduijn 2003	152/197	143/192		74.23%	1.08[0.86,1.35]
Dunlop MOPP 1998*	5/13	5/12		2.52%	0.96[0.28,3.31]
Dunlop MOPP/EVAP 98*	7/14	5/11		2.98%	1.41[0.45,4.41]





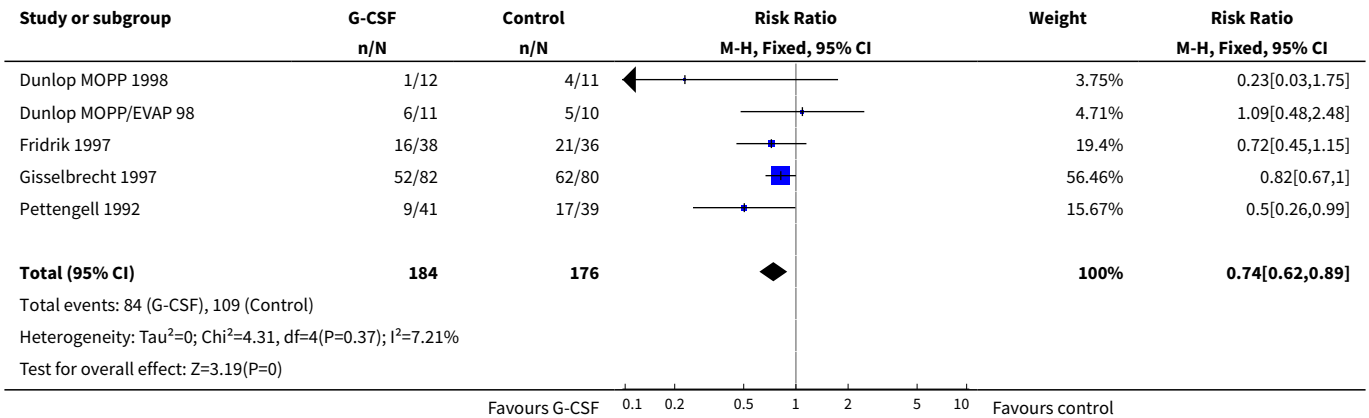
Study or subgroup	G(M)-CSF n/N	Control n/N	Peto Odds Ratio 95% CI	Weight	Peto Odds Ratio 95% CI
Fridrik 1997*	15/38	12/36		6.79%	1.22[0.57,2.59]
Gerhartz 1993	31/87	23/89		11.28%	1.21[0.67,2.18]
Total (95% CI)	**366**	**352**		**100%**	**1.11[0.91,1.35]**
Total events: 216 (G(M)-CSF), 191 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.55, df=5(P=0.99); I^2=0%					
Test for overall effect: Z=1.06(P=0.29)					

Analysis 1.3. Comparison 1 G-CSF/GM-CSF versus control, Outcome 3 Neutropenia.



Study or subgroup	G(M)-CSF n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aglietta 2000*	14/30	17/26		4.79%	0.71[0.44,1.15]
Cunningham*	7/18	5/19		1.28%	1.48[0.57,3.82]
Fridrik 1997*	24/38	26/36		7.02%	0.87[0.64,1.2]
Gisselbrecht 1997	43/82	60/80		15.98%	0.7[0.55,0.89]
Pettengell 1992	13/41	28/39		7.55%	0.44[0.27,0.72]
Zinzani 1997	18/77	40/72		10.87%	0.42[0.27,0.66]
Ösby CHOP 2003	56/101	93/104		24.1%	0.62[0.51,0.75]
Ösby CNOP 2003	80/125	108/125		28.41%	0.74[0.64,0.86]
Total (95% CI)	**512**	**501**		**100%**	**0.67[0.6,0.73]**
Total events: 255 (G(M)-CSF), 377 (Control)					
Heterogeneity: Tau^2=0; Chi^2=14.98, df=7(P=0.04); I^2=53.27%					
Test for overall effect: Z=8.23(P<0.0001)					

Analysis 1.4. Comparison 1 G-CSF/GM-CSF versus control, Outcome 4 Febrile Neutropenia, ANC < 1000.



Study or subgroup	G-CSF n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dunlop MOPP 1998	1/12	4/11		3.75%	0.23[0.03,1.75]
Dunlop MOPP/EVAP 98	6/11	5/10		4.71%	1.09[0.48,2.48]
Fridrik 1997	16/38	21/36		19.4%	0.72[0.45,1.15]
Gisselbrecht 1997	52/82	62/80		56.46%	0.82[0.67,1]
Pettengell 1992	9/41	17/39		15.67%	0.5[0.26,0.99]
Total (95% CI)	**184**	**176**		**100%**	**0.74[0.62,0.89]**
Total events: 84 (G-CSF), 109 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.31, df=4(P=0.37); I^2=7.21%					
Test for overall effect: Z=3.19(P=0)					

Analysis 1.5. Comparison 1 G-CSF/GM-CSF versus control, Outcome 5 Febrile Neutropenia, ANC < 500.

Study or subgroup	G-CSF n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Zinzani 1997*	18/77	40/72		26.57%	0.42[0.27,0.66]
Ösby CHOP 2003	34/101	52/104		32.93%	0.67[0.48,0.94]
Ösby CNOP 2003	40/125	63/125		40.49%	0.63[0.47,0.86]
Total (95% CI)	**303**	**301**		**100%**	**0.59[0.48,0.72]**
Total events: 92 (G-CSF), 155 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.94, df=2(P=0.23); I^2=31.99%					
Test for overall effect: Z=5.09(P<0.0001)					

Analysis 1.6. Comparison 1 G-CSF/GM-CSF versus control, Outcome 6 Infection.

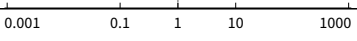
Study or subgroup	G(M)-CSF n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aglietta 2000*	6/30	6/26		2.39%	0.87[0.32,2.36]
Bastion ACVBP 1993	19/30	22/29		8.32%	0.83[0.59,1.17]
Bastion VIMMM 1993	18/30	16/30		5.95%	1.13[0.72,1.75]
Björkholm 1999	70/217	102/216		38.02%	0.68[0.54,0.87]
Dunlop MOPP 1998	7/13	8/12		3.09%	0.81[0.42,1.54]
Dunlop MOPP/EVAP 98	9/12	7/10		2.84%	1.07[0.64,1.8]
Fridrik 1997	14/38	19/36		7.26%	0.7[0.42,1.17]
Gerhartz 1993	27/87	36/85		13.54%	0.73[0.49,1.09]
Pettengell 1992	7/41	5/39		1.91%	1.33[0.46,3.85]
Souêtre 1994	20/82	29/80		10.92%	0.67[0.42,1.09]
Zinzani 1997	4/77	15/72		5.77%	0.25[0.09,0.72]
Total (95% CI)	**657**	**635**		**100%**	**0.74[0.64,0.85]**
Total events: 201 (G(M)-CSF), 265 (Control)					
Heterogeneity: Tau^2=0; Chi^2=12.02, df=10(P=0.28); I^2=16.79%					
Test for overall effect: Z=4.28(P<0.0001)					

Analysis 1.7. Comparison 1 G-CSF/GM-CSF versus control, Outcome 7 Parenteral antibiotic treatment.

Study or subgroup	G(M)-CSF n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aglietta 2000*	2/30	4/26		10.52%	0.43[0.09,2.18]
Fridrik 1997	23/38	18/36		45.36%	1.21[0.8,1.83]
Pettengell 1992	9/41	12/39		30.18%	0.71[0.34,1.5]
Zinzani 1997	0/77	5/72		13.94%	0.09[0,1.51]
Total (95% CI)	**186**	**173**		**100%**	**0.82[0.57,1.18]**
Total events: 34 (G(M)-CSF), 39 (Control)					
Heterogeneity: Tau^2=0; Chi^2=6.47, df=3(P=0.09); I^2=53.6%					
Test for overall effect: Z=1.07(P=0.28)					

Analysis 1.8. Comparison 1 G-CSF/GM-CSF versus control, Outcome 8 Overall mortality during chemotherapy.

Study or subgroup	G-/GM-CSF n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aglietta 2000	1/30	2/26		5.43%	0.43[0.04,4.51]
Avilés 1994*	1/20	2/22		4.83%	0.55[0.05,5.61]
Bastion 1993	7/59	6/60		15.09%	1.19[0.42,3.32]
Cunningham*	0/18	0/21			Not estimable
Doorduijn 2003	11/197	18/192		46.23%	0.6[0.29,1.23]
Dunlop MOPP 1998*	0/13	1/12		3.94%	0.31[0.01,6.94]
Dunlop MOPP/EVAP 98*	1/14	0/11		1.41%	2.4[0.11,53.77]
Fridrik 1997*	6/42	2/43		5.01%	3.07[0.66,14.37]
Gisselbrecht 1997	3/81	3/80		7.65%	0.99[0.21,4.75]
Pettengell 1992	6/41	4/39		10.4%	1.43[0.44,4.67]
Zinzani 1997*	0/77	0/72			Not estimable
Total (95% CI)	**592**	**578**		**100%**	**0.93[0.6,1.43]**
Total events: 36 (G-/GM-CSF), 38 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5.92, df=8(P=0.66); I^2=0%					
Test for overall effect: Z=0.34(P=0.74)					



Favours G-/GM-CSF — Favours control

Analysis 1.9. Comparison 1 G-CSF/GM-CSF versus control, Outcome 9 Infection related mortality during chemotherapy.

Study or subgroup	G-/GM-CSF n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aglietta 2000*	1/30	0/26		2.53%	2.61[0.11,61.51]
Avilés 1994*	0/20	0/22			Not estimable
Burton CHOP 2006	2/192	4/195		18.81%	0.51[0.09,2.74]
Burton PMitCEBO 2006	1/195	5/202		23.28%	0.21[0.02,1.76]
Cunningham*	0/18	0/21			Not estimable
Doorduijn 2003	4/197	6/192		28.8%	0.65[0.19,2.27]
Dunlop MOPP 1998*	0/13	0/12			Not estimable
Dunlop MOPP/EVAP 98*	1/14	0/11		2.63%	2.4[0.11,53.77]
Fridrik 1997	6/42	1/43		4.68%	6.14[0.77,48.87]
Gisselbrecht 1997*	2/81	2/80		9.54%	0.99[0.14,6.84]
Pettengell 1992	2/41	2/39		9.72%	0.95[0.14,6.43]
Zinzani 1997*	0/77	0/72			Not estimable
Total (95% CI)	**920**	**915**		**100%**	**0.93[0.51,1.71]**
Total events: 19 (G-/GM-CSF), 20 (Control)					
Heterogeneity: Tau^2=0; Chi^2=6.67, df=7(P=0.46); I^2=0%					
Test for overall effect: Z=0.22(P=0.83)					

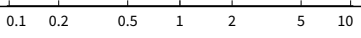
Favours G-/GM-CSF — Favours control

Analysis 1.10. Comparison 1 G-CSF/GM-CSF versus control, Outcome 10 Complete response.

Study or subgroup	G-/GM-CSF n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aglietta 2000	21/30	16/26		2.69%	1.14[0.78,1.67]
Avilés 1994	16/20	12/22		1.79%	1.47[0.94,2.28]
Burton 2006	201/387	199/397		30.78%	1.04[0.9,1.19]
Cunningham*	3/18	1/21		0.14%	3.5[0.4,30.77]
Doorduijn 2003	102/197	106/192		16.82%	0.94[0.78,1.13]
Dunlop MOPP 1998*	6/13	4/12		0.65%	1.38[0.51,3.74]
Dunlop MOPP/EVAP 98*	9/14	5/11		0.88%	1.41[0.66,3.01]
Engelhard 1994	56/87	52/85		8.24%	1.05[0.84,1.32]
Fridrik 1997	29/35	24/36		3.71%	1.24[0.94,1.64]
Gisselbrecht 1997	54/81	57/80		8.99%	0.94[0.76,1.15]
Zinzani 1997	46/77	42/72		6.8%	1.02[0.78,1.34]
Ösby CHOP 2003	62/101	61/104		9.42%	1.05[0.84,1.31]
Ösby CNOP 2003	51/125	58/125		9.09%	0.88[0.66,1.17]
Total (95% CI)	**1185**	**1183**		**100%**	**1.03[0.95,1.1]**
Total events: 656 (G-/GM-CSF), 637 (Control)					
Heterogeneity: Tau^2=0; Chi^2=9.84, df=12(P=0.63); I^2=0%					
Test for overall effect: Z=0.67(P=0.5)					

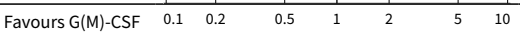
Analysis 1.11. Comparison 1 G-CSF/GM-CSF versus control, Outcome 11 Adverse events: bone pain.

Study or subgroup	G-/GM-CSF n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aglietta 2000	2/30	1/26		6.64%	1.73[0.17,18.04]
Avilés 1994	2/20	0/22		2.96%	5.48[0.28,107.62]
Fridrik 1997	2/42	0/43		3.06%	5.12[0.25,103.5]
Gerhartz 1993	8/89	6/87		37.61%	1.3[0.47,3.6]
Gisselbrecht 1997	18/81	4/80		24.94%	4.44[1.57,12.55]
Pettengell 1992	7/41	0/39		3.17%	14.29[0.84,242.02]
Zinzani 1997	2/77	0/72		3.2%	4.68[0.23,95.84]
Ösby CHOP 2003	10/101	2/104		12.21%	5.15[1.16,22.92]
Ösby CNOP 2003	5/125	1/125		6.2%	5[0.59,42.19]
Total (95% CI)	**606**	**598**		**100%**	**3.57[2.09,6.12]**
Total events: 56 (G-/GM-CSF), 14 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5.73, df=8(P=0.68); I^2=0%					
Test for overall effect: Z=4.64(P<0.0001)					



Analysis 1.12. Comparison 1 G-CSF/GM-CSF versus control, Outcome 12 Adverse events: thrombosis and related complications (TIA, MI, cerebral non-hemorhagic infarction).

Study or subgroup	G(M)-CSF n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aglietta 2000	1/30	0/26		5.87%	2.61[0.11,61.51]
Dunlop MOPP/EVAP 98	1/14	0/14		5.5%	3[0.13,67.91]
Fridrik 1997*	0/42	1/43		16.3%	0.34[0.01,8.14]
Gerhartz 1993	6/89	6/87		66.7%	0.98[0.33,2.91]
Pettengell 1992	2/41	0/39		5.63%	4.76[0.24,96.16]
Total (95% CI)	**216**	**209**		**100%**	**1.29[0.56,3.01]**
Total events: 10 (G(M)-CSF), 7 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.12, df=4(P=0.71); I^2=0%					
Test for overall effect: Z=0.6(P=0.55)					



Analysis 1.13. Comparison 1 G-CSF/GM-CSF versus control, Outcome 13 Adverse events: skin rash.

Study or subgroup	G-/GM-CSF n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aglietta 2000	10/30	2/26		51.44%	4.33[1.04,18.01]
Gerhartz 1993	23/89	2/87		48.56%	11.24[2.73,46.25]
Total (95% CI)	**119**	**113**		**100%**	**7.69[2.84,20.82]**
Total events: 33 (G-/GM-CSF), 4 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.9, df=1(P=0.34); I^2=0%					
Test for overall effect: Z=4.01(P<0.0001)					

Analysis 1.14. Comparison 1 G-CSF/GM-CSF versus control, Outcome 14 Adverse events: injection site reaction.

Study or subgroup	G-/GM-CSF n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Gerhartz 1993	40/89	6/87		92.34%	6.52[2.91,14.58]
Gisselbrecht 1997	3/81	0/80		7.66%	6.91[0.36,131.75]
Total (95% CI)	**170**	**167**		**100%**	**6.55[3.01,14.25]**
Total events: 43 (G-/GM-CSF), 6 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.97); I^2=0%					
Test for overall effect: Z=4.74(P<0.0001)					

Analysis 1.15. Comparison 1 G-CSF/GM-CSF versus control, Outcome 15 Adverse events: myalgia.

Study or subgroup	GM-CSF n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aglietta 2000	3/30	1/26		3.65%	2.6[0.29,23.5]
Gerhartz 1993	25/89	28/87		96.35%	0.87[0.56,1.37]
Total (95% CI)	**119**	**113**		**100%**	**0.94[0.6,1.45]**
Total events: 28 (GM-CSF), 29 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.92, df=1(P=0.34); I^2=0%					
Test for overall effect: Z=0.3(P=0.77)					

Analysis 1.16. Comparison 1 G-CSF/GM-CSF versus control, Outcome 16 Adverse events: mucositis.

Study or subgroup	G-CSF n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Gisselbrecht 1997	14/81	17/80		43.39%	0.81[0.43,1.54]
Pettengell 1992	15/41	15/39		39%	0.95[0.54,1.67]
Ösby CHOP 2003	5/101	4/104		10%	1.29[0.36,4.66]
Ösby CNOP 2003	4/125	3/125		7.61%	1.33[0.3,5.84]
Total (95% CI)	**348**	**348**		**100%**	**0.95[0.64,1.41]**
Total events: 38 (G-CSF), 39 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.65, df=3(P=0.89); I^2=0%					
Test for overall effect: Z=0.24(P=0.81)					

Analysis 1.17. Comparison 1 G-CSF/GM-CSF versus control, Outcome 17 Adverse events: headache.

Study or subgroup	G-/GM-CSF n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Gerhartz 1993	7/89	6/87		1.14[0.4,3.26]
Gisselbrecht 1997	40/81	18/80		2.19[1.38,3.49]

Analysis 1.18. Comparison 1 G-CSF/GM-CSF versus control, Outcome 18 Withdrawals due to adverse events.

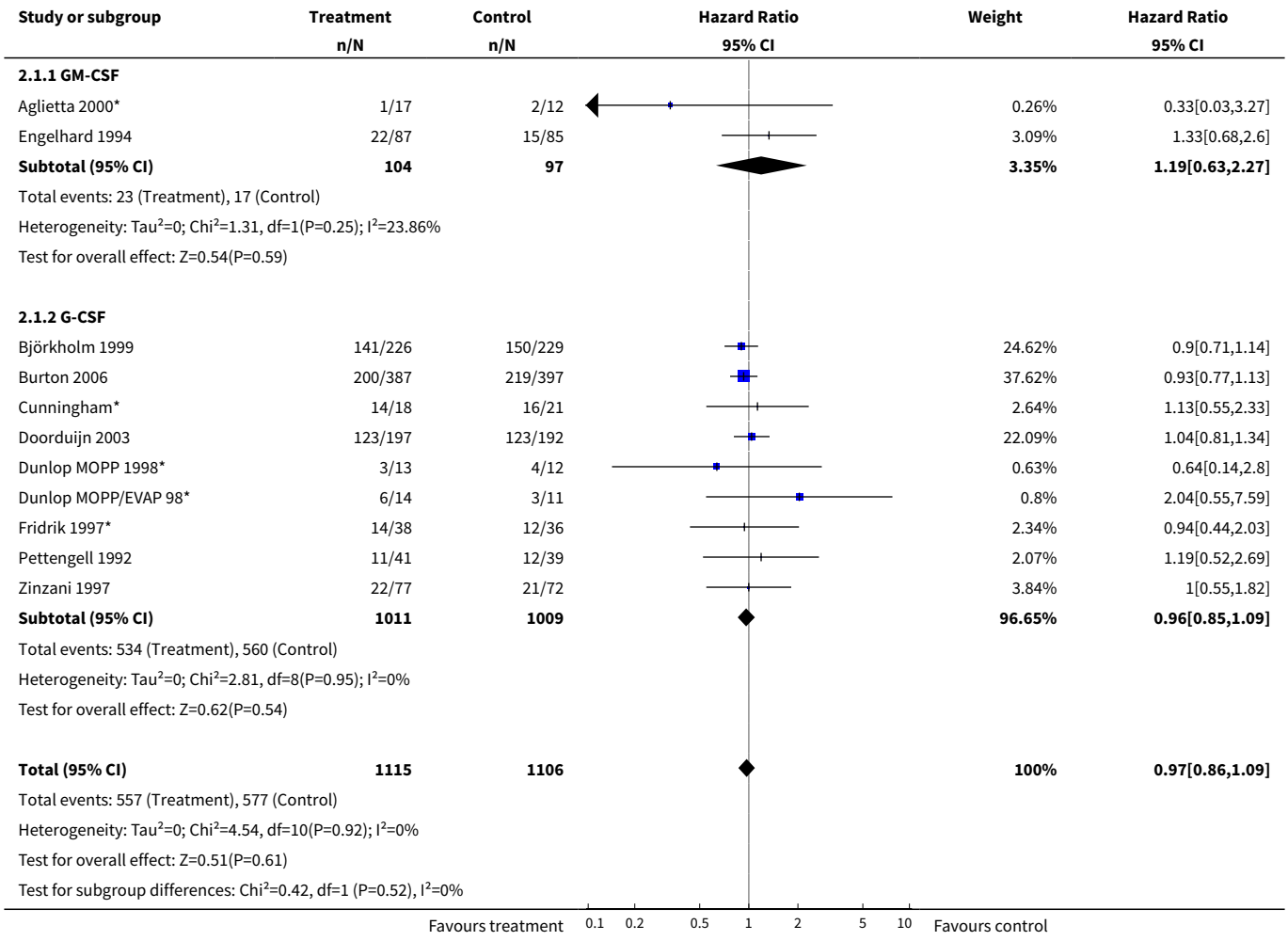
Study or subgroup	G-/GM-CSF n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.18.1 GM-CSF					
Aglietta 2000	6/30	0/26		9.56%	11.32[0.67,191.83]
Gerhartz 1993	22/87	5/85		90.44%	4.3[1.71,10.83]
Subtotal (95% CI)	**117**	**111**		**100%**	**4.97[2.07,11.96]**
Total events: 28 (G-/GM-CSF), 5 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.42, df=1(P=0.52); I^2=0%					
Test for overall effect: Z=3.58(P=0)					

Comparison 2. Sensitivity analysis: Overall survival

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 GM-CSF versus G-CSF	11	2221	Hazard Ratio (95% CI)	0.97 [0.86, 1.09]
1.1 GM-CSF	2	201	Hazard Ratio (95% CI)	1.19 [0.63, 2.27]
1.2 G-CSF	9	2020	Hazard Ratio (95% CI)	0.96 [0.85, 1.09]
2 HD versus NHL	11	2221	Hazard Ratio (95% CI)	0.97 [0.86, 1.09]
2.1 Hodgkin's disease	3	79	Hazard Ratio (95% CI)	1.00 [0.40, 2.46]
2.2 Non-Hodgkin's lymphoma	8	2142	Hazard Ratio (95% CI)	0.97 [0.86, 1.09]
3 Age	11	2221	Hazard Ratio (95% CI)	0.97 [0.86, 1.09]
3.1 Adults, all ages	7	444	Hazard Ratio (95% CI)	1.13 [0.80, 1.59]
3.2 Adults, age older 60	4	1777	Hazard Ratio (95% CI)	0.95 [0.84, 1.08]
4 Antibiotic prophylaxis	11	2221	Hazard Ratio (95% CI)	0.97 [0.86, 1.09]
4.1 No antibiotic prophylaxis given	8	1208	Hazard Ratio (95% CI)	0.99 [0.85, 1.16]
4.2 Antibiotic prophylaxis given	3	1013	Hazard Ratio (95% CI)	0.95 [0.79, 1.13]
5 Blinded versus open label studies	11	2221	Hazard Ratio (95% CI)	0.97 [0.86, 1.09]
5.1 Placebo controlled studies	2	201	Hazard Ratio (95% CI)	1.19 [0.63, 2.27]
5.2 Open label studies	9	2020	Hazard Ratio (95% CI)	0.96 [0.85, 1.09]
6 Concealed allocation versus concealment of allocation unclear	11	2221	Hazard Ratio (95% CI)	0.97 [0.86, 1.09]
6.1 Allocation concealed	9	1357	Hazard Ratio (95% CI)	0.99 [0.85, 1.15]
6.2 Method of allocation unclear	2	864	Hazard Ratio (95% CI)	0.94 [0.78, 1.14]
7 Size of studies	11	2221	Hazard Ratio (95% CI)	0.97 [0.86, 1.09]
7.1 Study size <100	6	272	Hazard Ratio (95% CI)	1.06 [0.71, 1.58]
7.2 Study size >100	5	1949	Hazard Ratio (95% CI)	0.96 [0.85, 1.09]

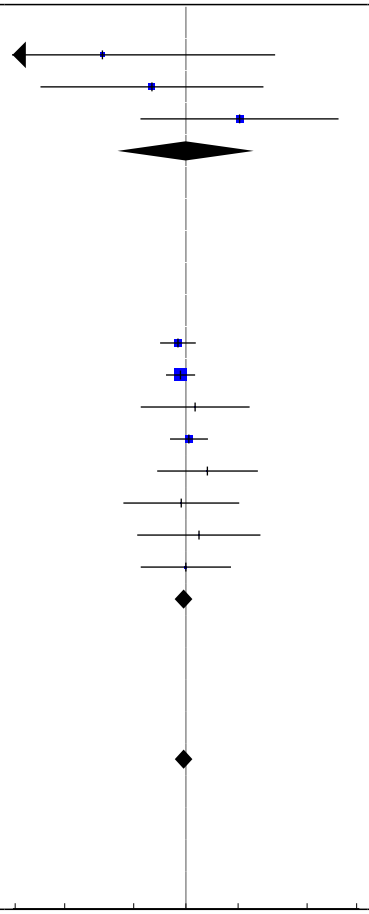
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Duration of follow-up	11	2221	Hazard Ratio (95% CI)	0.97 [0.86, 1.09]
8.1 Follow-up 1-2 years	3	401	Hazard Ratio (95% CI)	1.15 [0.78, 1.70]
8.2 Follow-up 2-5 years	4	1702	Hazard Ratio (95% CI)	0.95 [0.84, 1.08]
8.3 Follow-up 5-8 years	4	118	Hazard Ratio (95% CI)	1.08 [0.61, 1.89]

Analysis 2.1. Comparison 2 Sensitivity analysis: Overall survival, Outcome 1 GM-CSF versus G-CSF.



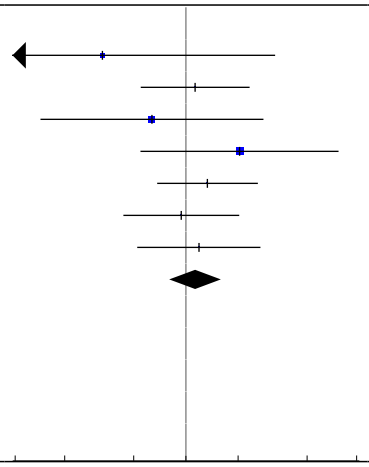
Analysis 2.2. Comparison 2 Sensitivity analysis: Overall survival, Outcome 2 HD versus NHL.

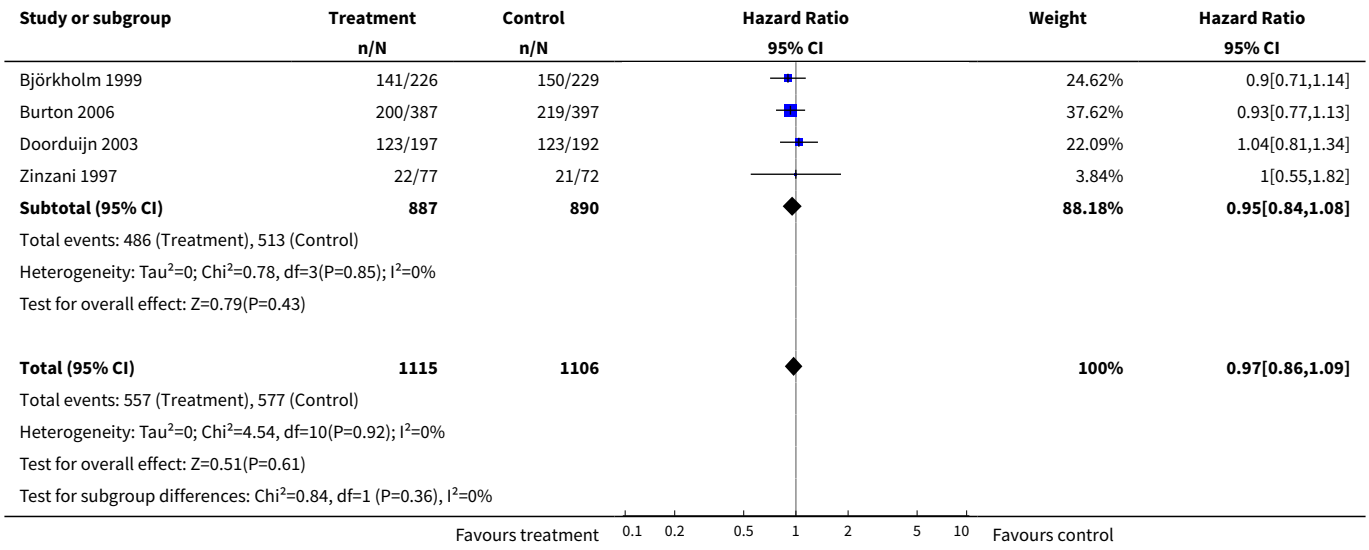
Study or subgroup	Treatment n/N	Control n/N	Hazard Ratio 95% CI	Weight	Hazard Ratio 95% CI
2.2.1 Hodgkin's disease					
Aglietta 2000*	1/17	2/12		0.26%	0.33[0.03,3.27]
Dunlop MOPP 1998*	3/13	4/12		0.63%	0.64[0.14,2.8]
Dunlop MOPP/EVAP 98*	6/14	3/11		0.8%	2.04[0.55,7.59]
Subtotal (95% CI)	**44**	**35**		**1.69%**	**1[0.4,2.46]**
Total events: 10 (Treatment), 9 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.38, df=2(P=0.3); I^2=15.96%					
Test for overall effect: Z=0.01(P=0.99)					
2.2.2 Non-Hodgkin's lymphoma					
Björkholm 1999	141/226	150/229		24.66%	0.9[0.71,1.14]
Burton 2006	199/387	218/397		37.52%	0.93[0.77,1.13]
Cunningham*	14/18	16/21		2.65%	1.13[0.55,2.33]
Doorduijn 2003	123/197	123/192		22.13%	1.04[0.81,1.34]
Engelhard 1994	22/87	15/85		3.09%	1.33[0.68,2.6]
Fridrik 1997*	14/38	12/36		2.34%	0.94[0.44,2.03]
Pettengell 1992	11/41	12/39		2.07%	1.19[0.52,2.69]
Zinzani 1997	22/77	21/72		3.85%	1[0.55,1.82]
Subtotal (95% CI)	**1071**	**1071**		**98.31%**	**0.97[0.86,1.09]**
Total events: 546 (Treatment), 567 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.16, df=7(P=0.95); I^2=0%					
Test for overall effect: Z=0.51(P=0.61)					
Total (95% CI)	**1115**	**1106**		**100%**	**0.97[0.86,1.09]**
Total events: 556 (Treatment), 576 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.54, df=10(P=0.92); I^2=0%					
Test for overall effect: Z=0.5(P=0.61)					
Test for subgroup differences: Chi^2=0, df=1 (P=0.95), I^2=0%					



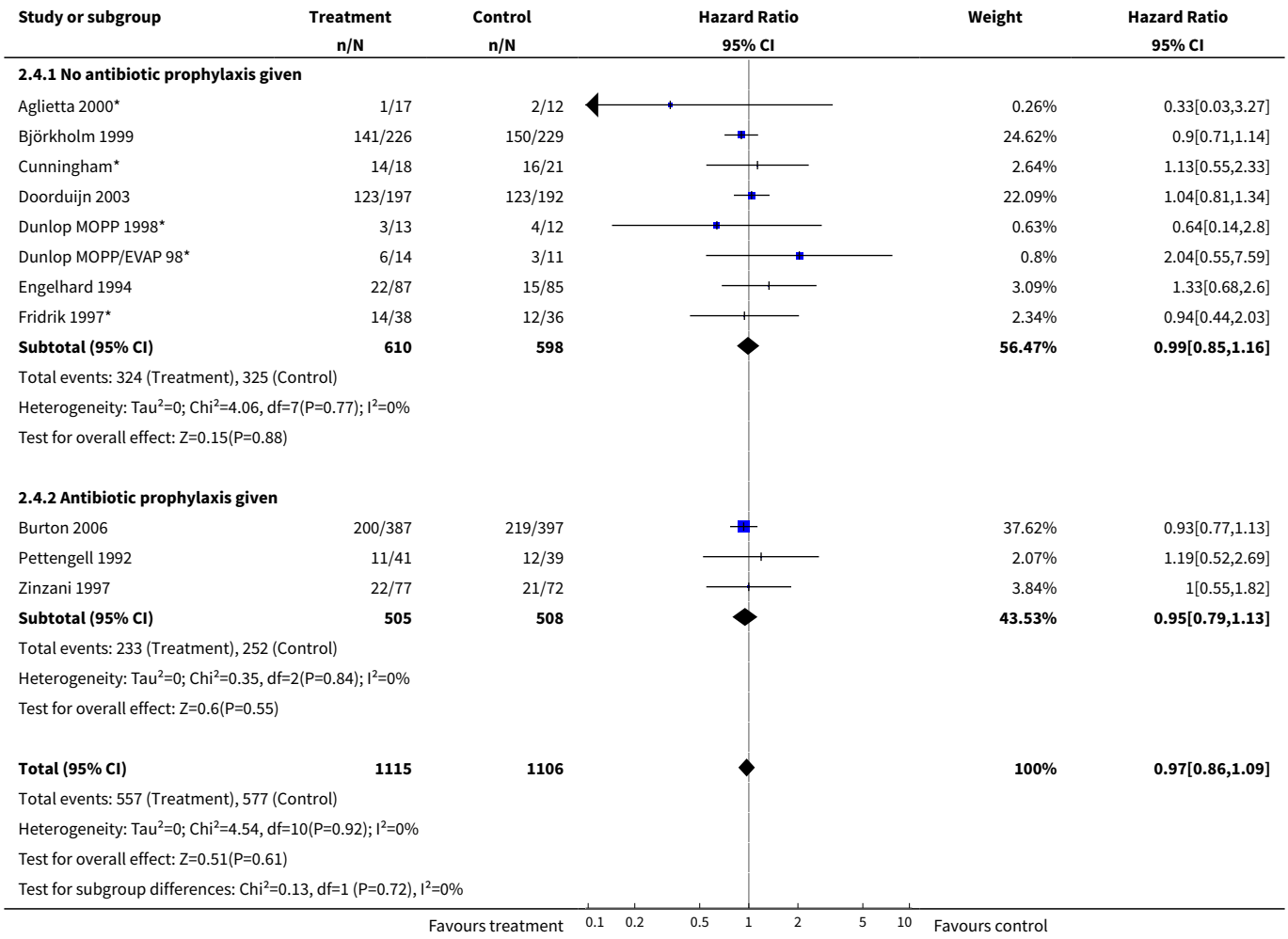
Analysis 2.3. Comparison 2 Sensitivity analysis: Overall survival, Outcome 3 Age.

Study or subgroup	Treatment n/N	Control n/N	Hazard Ratio 95% CI	Weight	Hazard Ratio 95% CI
2.3.1 Adults, all ages					
Aglietta 2000*	1/17	2/12		0.26%	0.33[0.03,3.27]
Cunningham*	14/18	16/21		2.64%	1.13[0.55,2.33]
Dunlop MOPP 1998*	3/13	4/12		0.63%	0.64[0.14,2.8]
Dunlop MOPP/EVAP 98*	6/14	3/11		0.8%	2.04[0.55,7.59]
Engelhard 1994	22/87	15/85		3.09%	1.33[0.68,2.6]
Fridrik 1997*	14/38	12/36		2.34%	0.94[0.44,2.03]
Pettengell 1992	11/41	12/39		2.07%	1.19[0.52,2.69]
Subtotal (95% CI)	**228**	**216**		**11.82%**	**1.13[0.8,1.59]**
Total events: 71 (Treatment), 64 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.92, df=6(P=0.82); I^2=0%					
Test for overall effect: Z=0.69(P=0.49)					
2.3.2 Adults, age older 60					

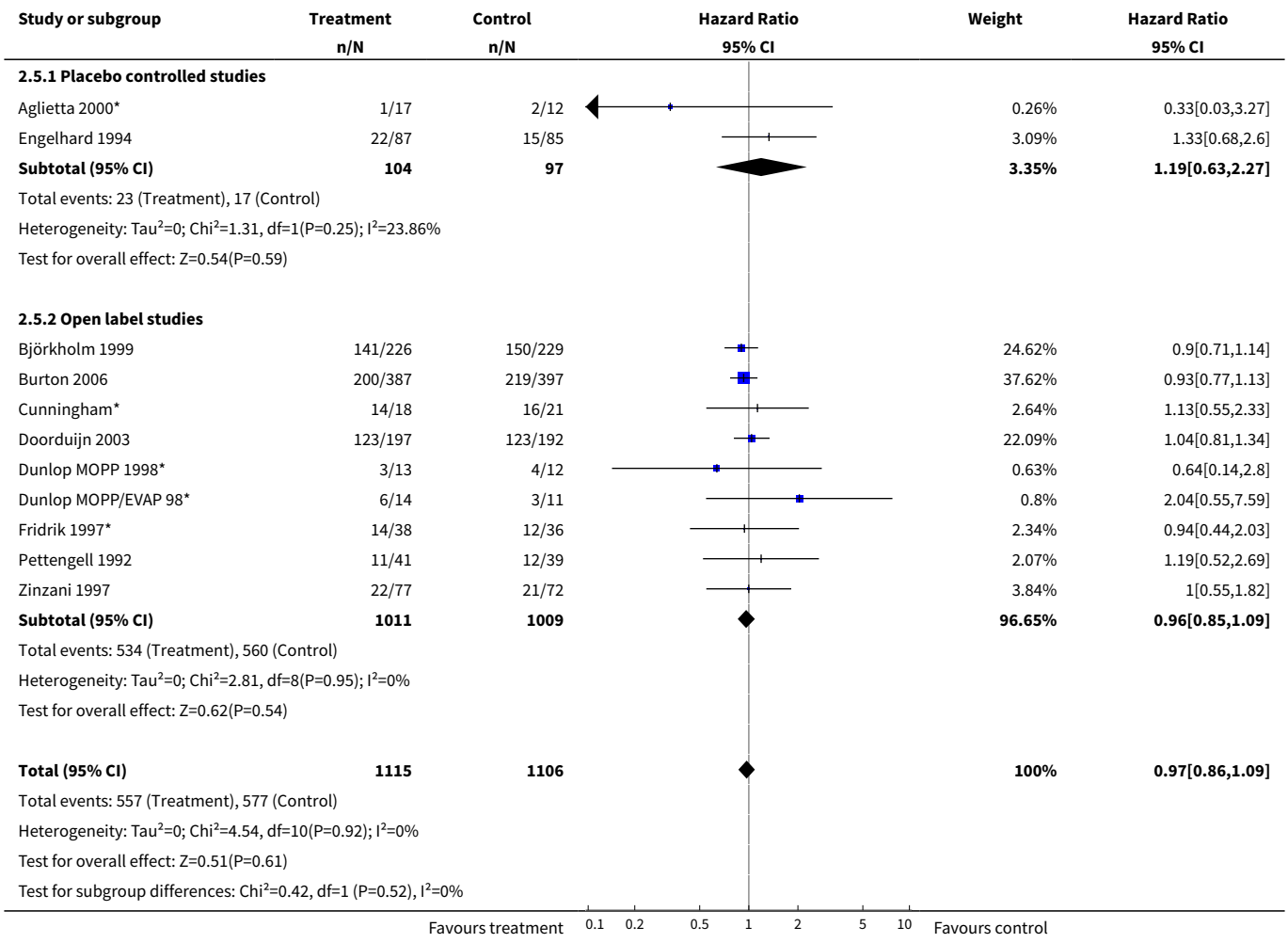




Analysis 2.4. Comparison 2 Sensitivity analysis: Overall survival, Outcome 4 Antibiotic prophylaxis.

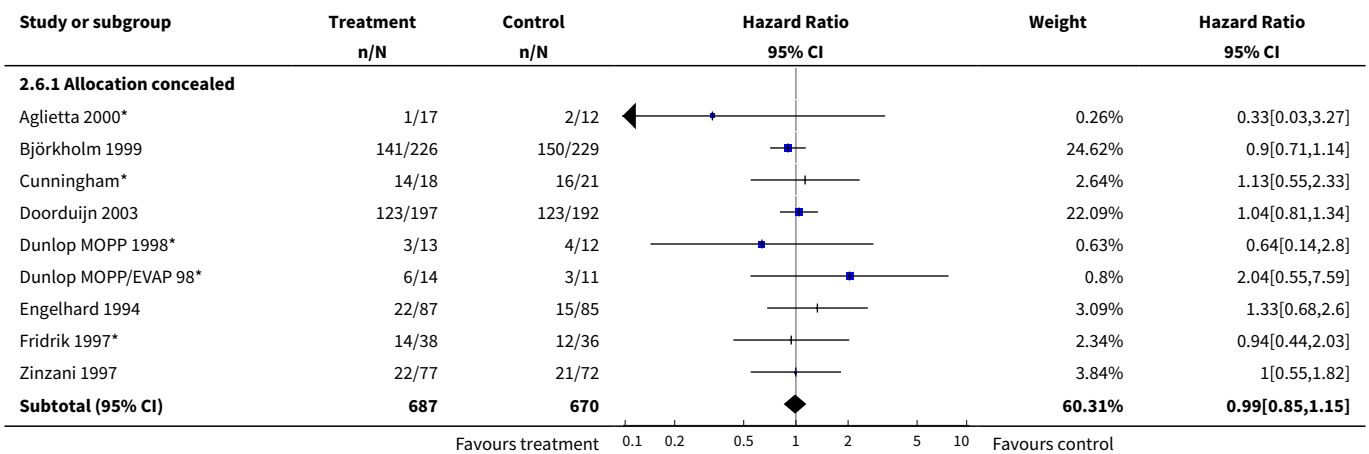


Analysis 2.5. Comparison 2 Sensitivity analysis: Overall survival, Outcome 5 Blinded versus open label studies.

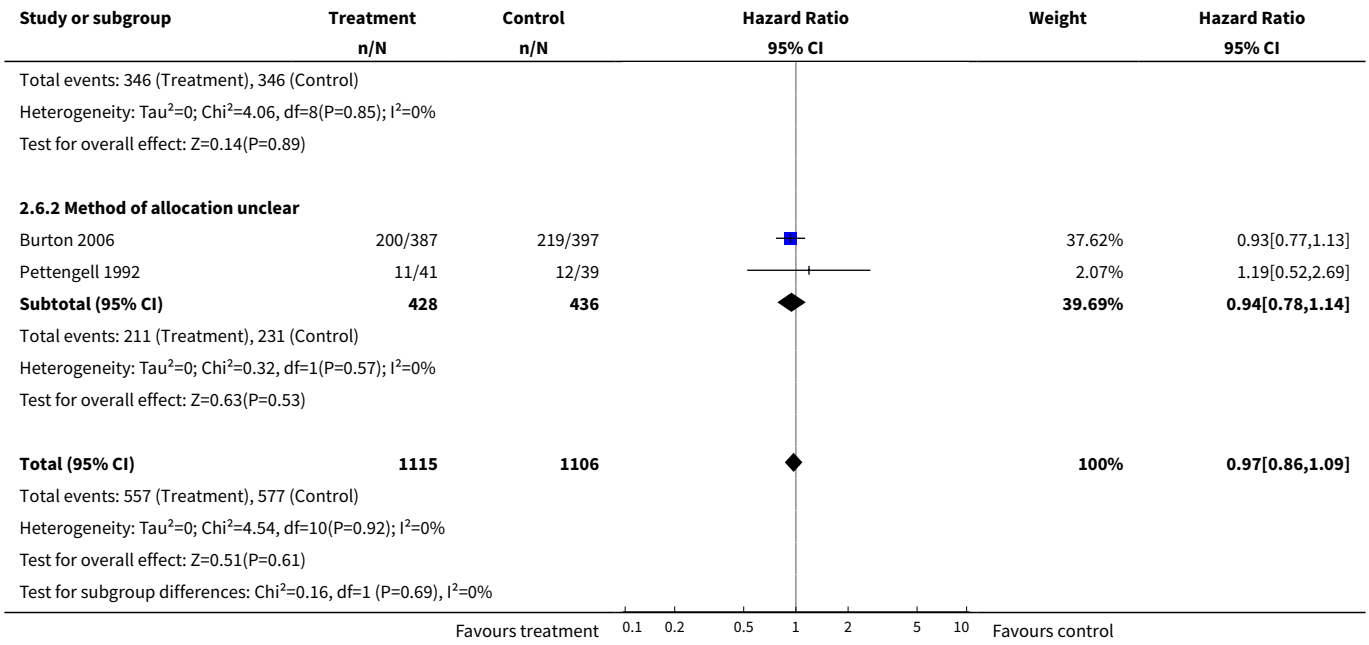


Study or subgroup	Treatment n/N	Control n/N	Hazard Ratio 95% CI	Weight	Hazard Ratio 95% CI
2.5.1 Placebo controlled studies					
Aglietta 2000*	1/17	2/12		0.26%	0.33[0.03,3.27]
Engelhard 1994	22/87	15/85		3.09%	1.33[0.68,2.6]
Subtotal (95% CI)	**104**	**97**		**3.35%**	**1.19[0.63,2.27]**
Total events: 23 (Treatment), 17 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.31, df=1(P=0.25); I^2=23.86%					
Test for overall effect: Z=0.54(P=0.59)					
2.5.2 Open label studies					
Björkholm 1999	141/226	150/229		24.62%	0.9[0.71,1.14]
Burton 2006	200/387	219/397		37.62%	0.93[0.77,1.13]
Cunningham*	14/18	16/21		2.64%	1.13[0.55,2.33]
Doorduijn 2003	123/197	123/192		22.09%	1.04[0.81,1.34]
Dunlop MOPP 1998*	3/13	4/12		0.63%	0.64[0.14,2.8]
Dunlop MOPP/EVAP 98*	6/14	3/11		0.8%	2.04[0.55,7.59]
Fridrik 1997*	14/38	12/36		2.34%	0.94[0.44,2.03]
Pettengell 1992	11/41	12/39		2.07%	1.19[0.52,2.69]
Zinzani 1997	22/77	21/72		3.84%	1[0.55,1.82]
Subtotal (95% CI)	**1011**	**1009**		**96.65%**	**0.96[0.85,1.09]**
Total events: 534 (Treatment), 560 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.81, df=8(P=0.95); I^2=0%					
Test for overall effect: Z=0.62(P=0.54)					
Total (95% CI)	**1115**	**1106**		**100%**	**0.97[0.86,1.09]**
Total events: 557 (Treatment), 577 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.54, df=10(P=0.92); I^2=0%					
Test for overall effect: Z=0.51(P=0.61)					
Test for subgroup differences: Chi^2=0.42, df=1 (P=0.52), I^2=0%					

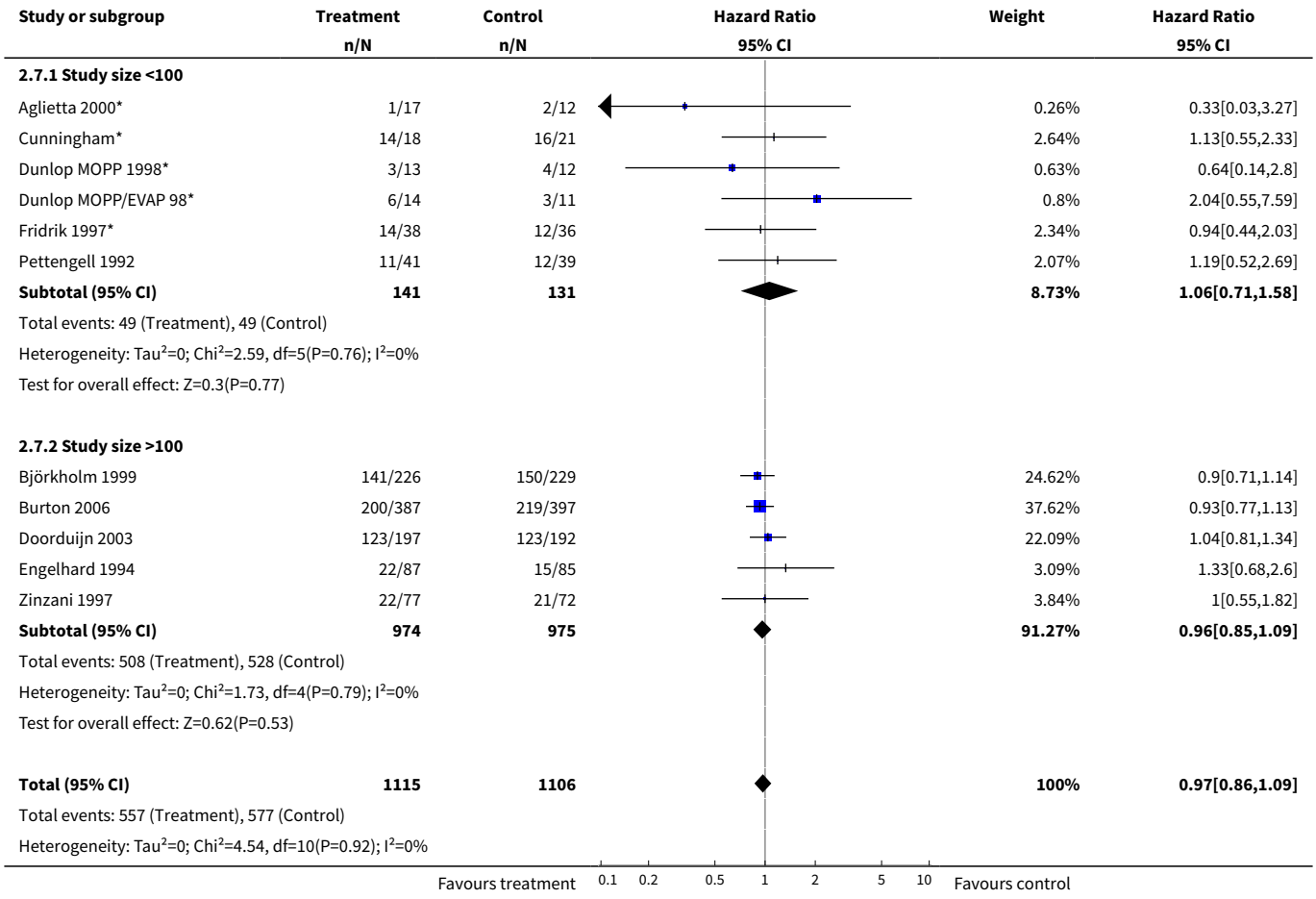
Analysis 2.6. Comparison 2 Sensitivity analysis: Overall survival, Outcome 6 Concealed allocation versus concealment of allocation unclear.



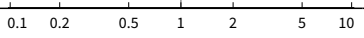
Study or subgroup	Treatment n/N	Control n/N	Hazard Ratio 95% CI	Weight	Hazard Ratio 95% CI
2.6.1 Allocation concealed					
Aglietta 2000*	1/17	2/12		0.26%	0.33[0.03,3.27]
Björkholm 1999	141/226	150/229		24.62%	0.9[0.71,1.14]
Cunningham*	14/18	16/21		2.64%	1.13[0.55,2.33]
Doorduijn 2003	123/197	123/192		22.09%	1.04[0.81,1.34]
Dunlop MOPP 1998*	3/13	4/12		0.63%	0.64[0.14,2.8]
Dunlop MOPP/EVAP 98*	6/14	3/11		0.8%	2.04[0.55,7.59]
Engelhard 1994	22/87	15/85		3.09%	1.33[0.68,2.6]
Fridrik 1997*	14/38	12/36		2.34%	0.94[0.44,2.03]
Zinzani 1997	22/77	21/72		3.84%	1[0.55,1.82]
Subtotal (95% CI)	**687**	**670**		**60.31%**	**0.99[0.85,1.15]**



Analysis 2.7. Comparison 2 Sensitivity analysis: Overall survival, Outcome 7 Size of studies.

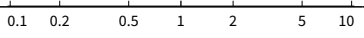


Study or subgroup	Treatment n/N	Control n/N	Hazard Ratio 95% CI	Weight	Hazard Ratio 95% CI
Test for overall effect: Z=0.51(P=0.61)					
Test for subgroup differences: Chi²=0.22, df=1 (P=0.64), I²=0%					



Analysis 2.8. Comparison 2 Sensitivity analysis: Overall survival, Outcome 8 Duration of follow-up.

Study or subgroup	Treatment n/N	Control n/N	Hazard Ratio 95% CI	Weight	Hazard Ratio 95% CI
2.8.1 Follow-up 1-2 years					
Engelhard 1994	22/87	15/85		3.09%	1.33[0.68,2.6]
Pettengell 1992	11/41	12/39		2.07%	1.19[0.52,2.69]
Zinzani 1997	22/77	21/72		3.84%	1[0.55,1.82]
Subtotal (95% CI)	**205**	**196**		**9%**	**1.15[0.78,1.7]**
Total events: 55 (Treatment), 48 (Control)					
Heterogeneity: Tau²=0; Chi²=0.4, df=2(P=0.82); I²=0%					
Test for overall effect: Z=0.69(P=0.49)					
2.8.2 Follow-up 2-5 years					
Björkholm 1999	141/226	150/229		24.62%	0.9[0.71,1.14]
Burton 2006	200/387	219/397		37.62%	0.93[0.77,1.13]
Doorduijn 2003	123/197	123/192		22.09%	1.04[0.81,1.34]
Fridrik 1997*	14/38	12/36		2.34%	0.94[0.44,2.03]
Subtotal (95% CI)	**848**	**854**		**86.67%**	**0.95[0.84,1.08]**
Total events: 478 (Treatment), 504 (Control)					
Heterogeneity: Tau²=0; Chi²=0.75, df=3(P=0.86); I²=0%					
Test for overall effect: Z=0.82(P=0.41)					
2.8.3 Follow-up 5-8 years					
Aglietta 2000*	1/17	2/12		0.26%	0.33[0.03,3.27]
Cunningham*	14/18	16/21		2.64%	1.13[0.55,2.33]
Dunlop MOPP 1998*	3/13	4/12		0.63%	0.64[0.14,2.8]
Dunlop MOPP/EVAP 98*	6/14	3/11		0.8%	2.04[0.55,7.59]
Subtotal (95% CI)	**62**	**56**		**4.33%**	**1.08[0.61,1.89]**
Total events: 24 (Treatment), 25 (Control)					
Heterogeneity: Tau²=0; Chi²=2.43, df=3(P=0.49); I²=0%					
Test for overall effect: Z=0.25(P=0.8)					
Total (95% CI)	**1115**	**1106**		**100%**	**0.97[0.86,1.09]**
Total events: 557 (Treatment), 577 (Control)					
Heterogeneity: Tau²=0; Chi²=4.54, df=10(P=0.92); I²=0%					
Test for overall effect: Z=0.51(P=0.61)					
Test for subgroup differences: Chi²=0.96, df=1 (P=0.62), I²=0%					



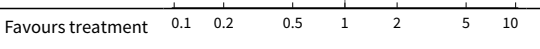
Comparison 3. Sensitivity analysis: Neutropenia

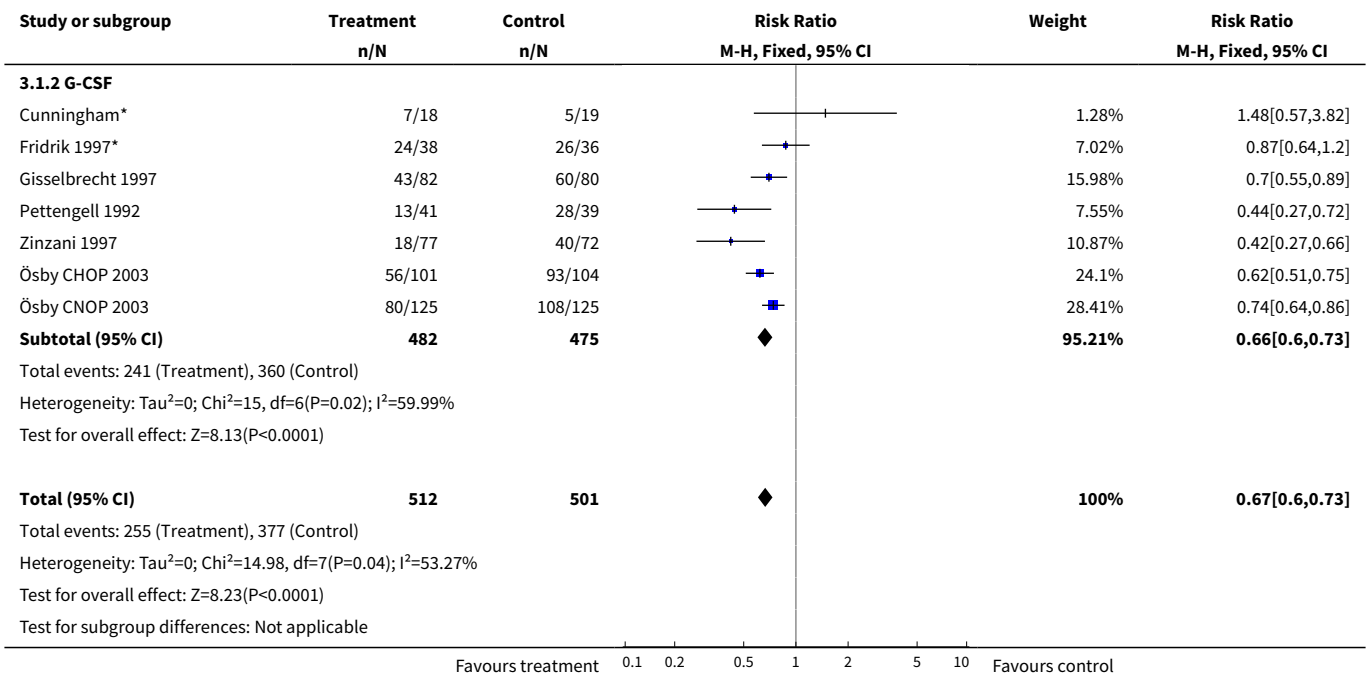
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 G-CSF versus GM-CSF	8	1013	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.60, 0.73]
1.1 GM-CSF	1	56	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.44, 1.15]
1.2 G-CSF	7	957	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.60, 0.73]
2 HD versus NHL	8	1013	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.60, 0.73]
2.1 Hodgkin's disease	1	56	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.44, 1.15]
2.2 Non-Hodgkin's lymphoma	7	957	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.60, 0.73]
3 Age	8	1013	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.60, 0.73]
3.1 Adults, all age groups	5	409	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.60, 0.84]
3.2 Adults, age older 60	3	604	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.57, 0.72]
4 Haematotoxicity	8	1013	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.60, 0.73]
4.1 Rate of neutropenia in the control group >70%	5	771	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.62, 0.75]
4.2 Rate of neutropenia in the control group 50%-70%	2	205	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.37, 0.71]
4.3 Rate of neutropenia in the control gorup < 50%	1	37	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [0.57, 3.82]
5 Use of antibiotic prophylaxis	8	1013	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.60, 0.73]
5.1 No antibiotic prophylaxis given	6	784	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.65, 0.79]
5.2 Antibiotic prophylaxis given	2	229	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.31, 0.60]
6 Blinded versus openlabel studies	8	1013	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.60, 0.73]
6.1 Placebo controlled studies	2	218	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.57, 0.87]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.2 Open label studies	6	795	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.59, 0.73]
7 Concealed versus unclear method of allocation	8	1013	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.60, 0.73]
7.1 Allocation concealed	7	933	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.62, 0.75]
7.2 Method of allocation unclear	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.27, 0.72]
8 Published and reported data versus unpublished or unreported data	8	1013	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.60, 0.73]
8.1 Unreported and unpublished data	3	167	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.67, 1.13]
8.2 Published and reported data	5	846	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.57, 0.70]
9 Size of study	8	1013	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.60, 0.73]
9.1 Study size <100 patients	4	247	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.57, 0.90]
9.2 Study size > 100 patients	4	766	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.59, 0.73]
10 Worst case-best case	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Worst case	8	1035	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.62, 0.76]
10.2 Best case	8	1035	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.59, 0.71]

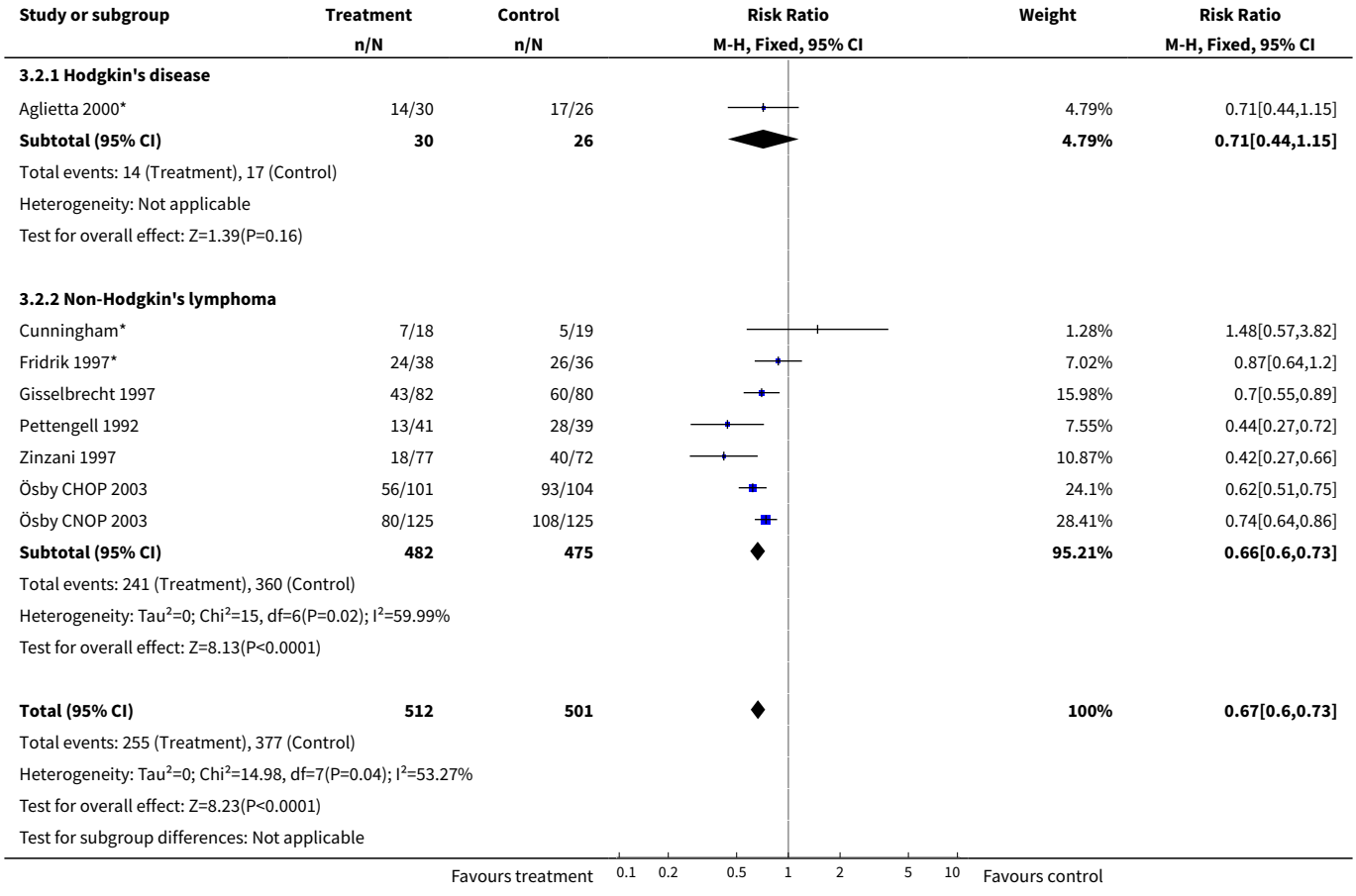
Analysis 3.1. Comparison 3 Sensitivity analysis: Neutropenia, Outcome 1 G-CSF versus GM-CSF.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.1.1 GM-CSF					
Aglietta 2000*	14/30	17/26		4.79%	0.71[0.44,1.15]
Subtotal (95% CI)	**30**	**26**		**4.79%**	**0.71[0.44,1.15]**
Total events: 14 (Treatment), 17 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.39(P=0.16)					



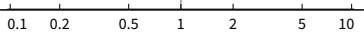


Analysis 3.2. Comparison 3 Sensitivity analysis: Neutropenia, Outcome 2 HD versus NHL.



Analysis 3.3. Comparison 3 Sensitivity analysis: Neutropenia, Outcome 3 Age.

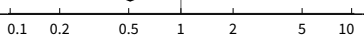
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.3.1 Adults, all age groups					
Aglietta 2000*	14/30	17/26		4.79%	0.71[0.44,1.15]
Cunningham*	7/18	5/19		1.28%	1.48[0.57,3.82]
Fridrik 1997*	24/38	26/36		7.02%	0.87[0.64,1.2]
Gisselbrecht 1997	43/82	60/80		15.98%	0.7[0.55,0.89]
Pettengell 1992	13/41	28/39		7.55%	0.44[0.27,0.72]
Subtotal (95% CI)	**209**	**200**		**36.62%**	**0.71[0.6,0.84]**
Total events: 101 (Treatment), 136 (Control)					
Heterogeneity: Tau^2=0; Chi^2=7.58, df=4(P=0.11); I^2=47.25%					
Test for overall effect: Z=4.03(P<0.0001)					
3.3.2 Adults, age older 60					
Zinzani 1997	18/77	40/72		10.87%	0.42[0.27,0.66]
Ösby CHOP 2003	56/101	93/104		24.1%	0.62[0.51,0.75]
Ösby CNOP 2003	80/125	108/125		28.41%	0.74[0.64,0.86]
Subtotal (95% CI)	**303**	**301**		**63.38%**	**0.64[0.57,0.72]**
Total events: 154 (Treatment), 241 (Control)					
Heterogeneity: Tau^2=0; Chi^2=7.1, df=2(P=0.03); I^2=71.83%					
Test for overall effect: Z=7.39(P<0.0001)					
Total (95% CI)	**512**	**501**		**100%**	**0.67[0.6,0.73]**
Total events: 255 (Treatment), 377 (Control)					
Heterogeneity: Tau^2=0; Chi^2=14.98, df=7(P=0.04); I^2=53.27%					
Test for overall effect: Z=8.23(P<0.0001)					
Test for subgroup differences: Not applicable					



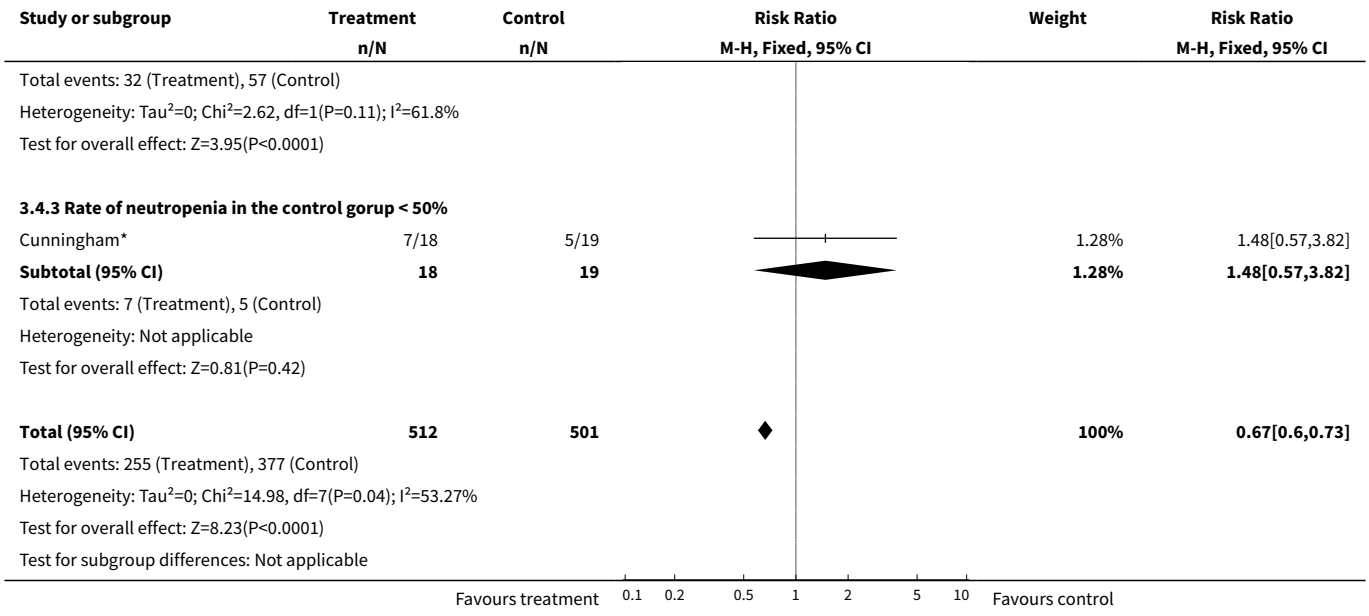
Favours treatment — Favours control

Analysis 3.4. Comparison 3 Sensitivity analysis: Neutropenia, Outcome 4 Haematotoxicity.

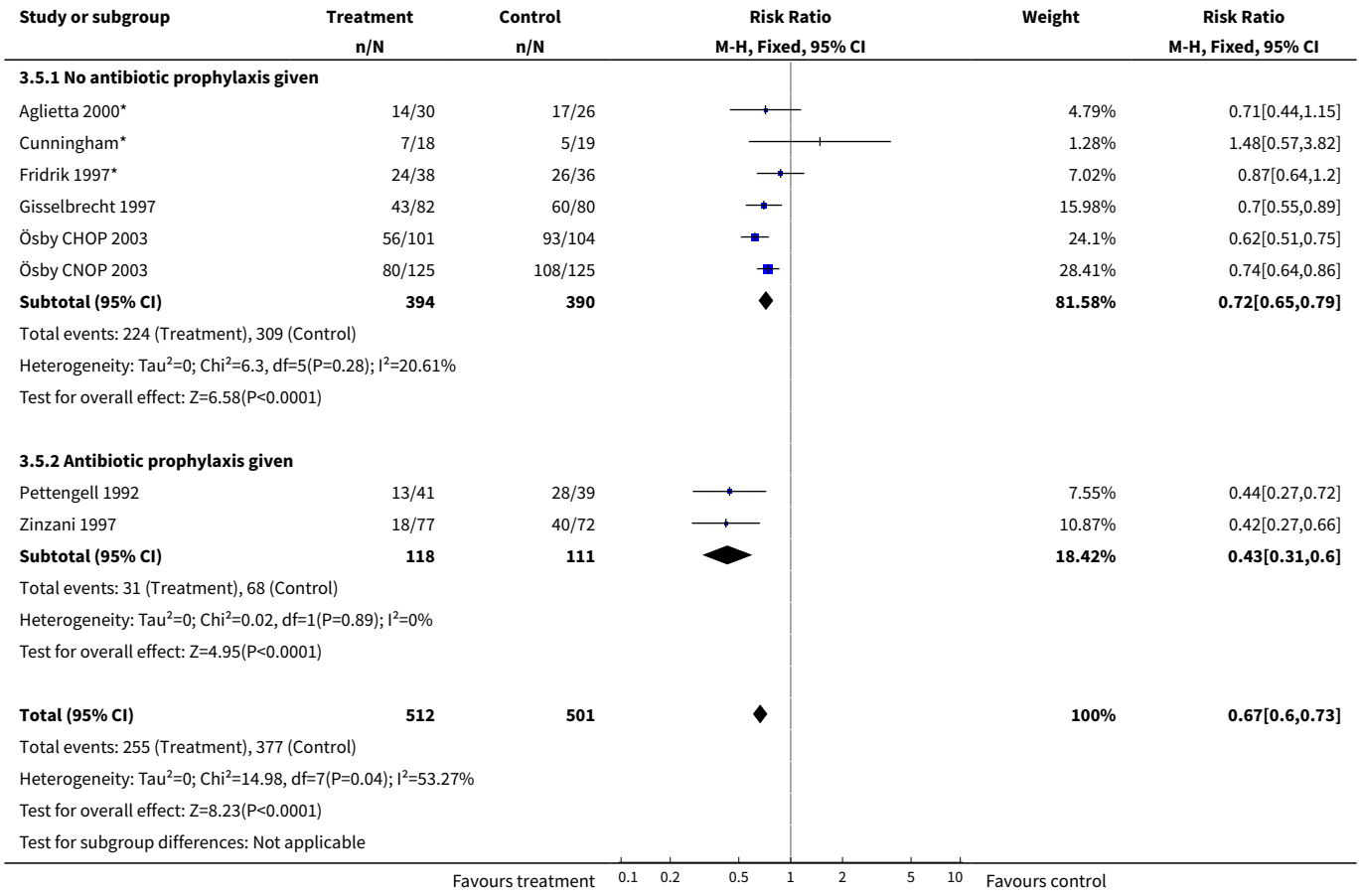
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.4.1 Rate of neutropenia in the control group >70%					
Fridrik 1997*	24/38	26/36		7.02%	0.87[0.64,1.2]
Gisselbrecht 1997	43/82	60/80		15.98%	0.7[0.55,0.89]
Pettengell 1992	13/41	28/39		7.55%	0.44[0.27,0.72]
Ösby CHOP 2003	56/101	93/104		24.1%	0.62[0.51,0.75]
Ösby CNOP 2003	80/125	108/125		28.41%	0.74[0.64,0.86]
Subtotal (95% CI)	**387**	**384**		**83.06%**	**0.68[0.62,0.75]**
Total events: 216 (Treatment), 315 (Control)					
Heterogeneity: Tau^2=0; Chi^2=7.62, df=4(P=0.11); I^2=47.49%					
Test for overall effect: Z=7.54(P<0.0001)					
3.4.2 Rate of neutropenia in the control group 50%-70%					
Aglietta 2000*	14/30	17/26		4.79%	0.71[0.44,1.15]
Zinzani 1997	18/77	40/72		10.87%	0.42[0.27,0.66]
Subtotal (95% CI)	**107**	**98**		**15.66%**	**0.51[0.37,0.71]**



Favours treatment — Favours control

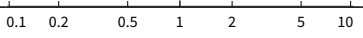


Analysis 3.5. Comparison 3 Sensitivity analysis: Neutropenia, Outcome 5 Use of antibiotic prophylaxis.



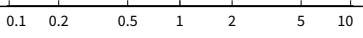
Analysis 3.6. Comparison 3 Sensitivity analysis: Neutropenia, Outcome 6 Blinded versus openlabel studies.

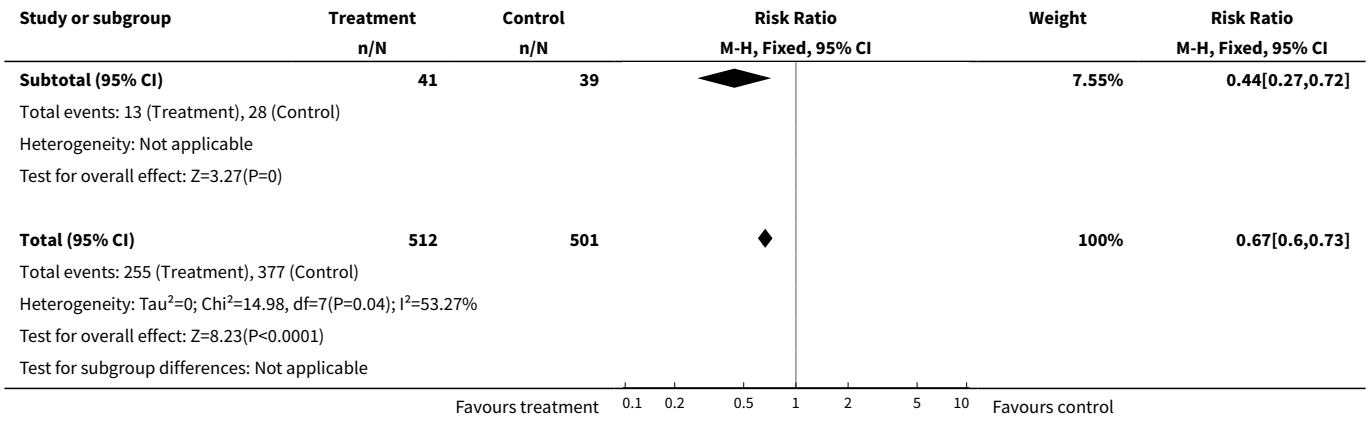
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.6.1 Placebo controlled studies					
Aglietta 2000*	14/30	17/26		4.79%	0.71[0.44,1.15]
Gisselbrecht 1997	43/82	60/80		15.98%	0.7[0.55,0.89]
Subtotal (95% CI)	**112**	**106**		**20.77%**	**0.7[0.57,0.87]**
Total events: 57 (Treatment), 77 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.94); I^2=0%					
Test for overall effect: Z=3.21(P=0)					
3.6.2 Open label studies					
Cunningham*	7/18	5/19		1.28%	1.48[0.57,3.82]
Fridrik 1997*	24/38	26/36		7.02%	0.87[0.64,1.2]
Pettengell 1992	13/41	28/39		7.55%	0.44[0.27,0.72]
Zinzani 1997	18/77	40/72		10.87%	0.42[0.27,0.66]
Ösby CHOP 2003	56/101	93/104		24.1%	0.62[0.51,0.75]
Ösby CNOP 2003	80/125	108/125		28.41%	0.74[0.64,0.86]
Subtotal (95% CI)	**400**	**395**		**79.23%**	**0.66[0.59,0.73]**
Total events: 198 (Treatment), 300 (Control)					
Heterogeneity: Tau^2=0; Chi^2=15.1, df=5(P=0.01); I^2=66.89%					
Test for overall effect: Z=7.62(P<0.0001)					
Total (95% CI)	**512**	**501**		**100%**	**0.67[0.6,0.73]**
Total events: 255 (Treatment), 377 (Control)					
Heterogeneity: Tau^2=0; Chi^2=14.98, df=7(P=0.04); I^2=53.27%					
Test for overall effect: Z=8.23(P<0.0001)					
Test for subgroup differences: Not applicable					



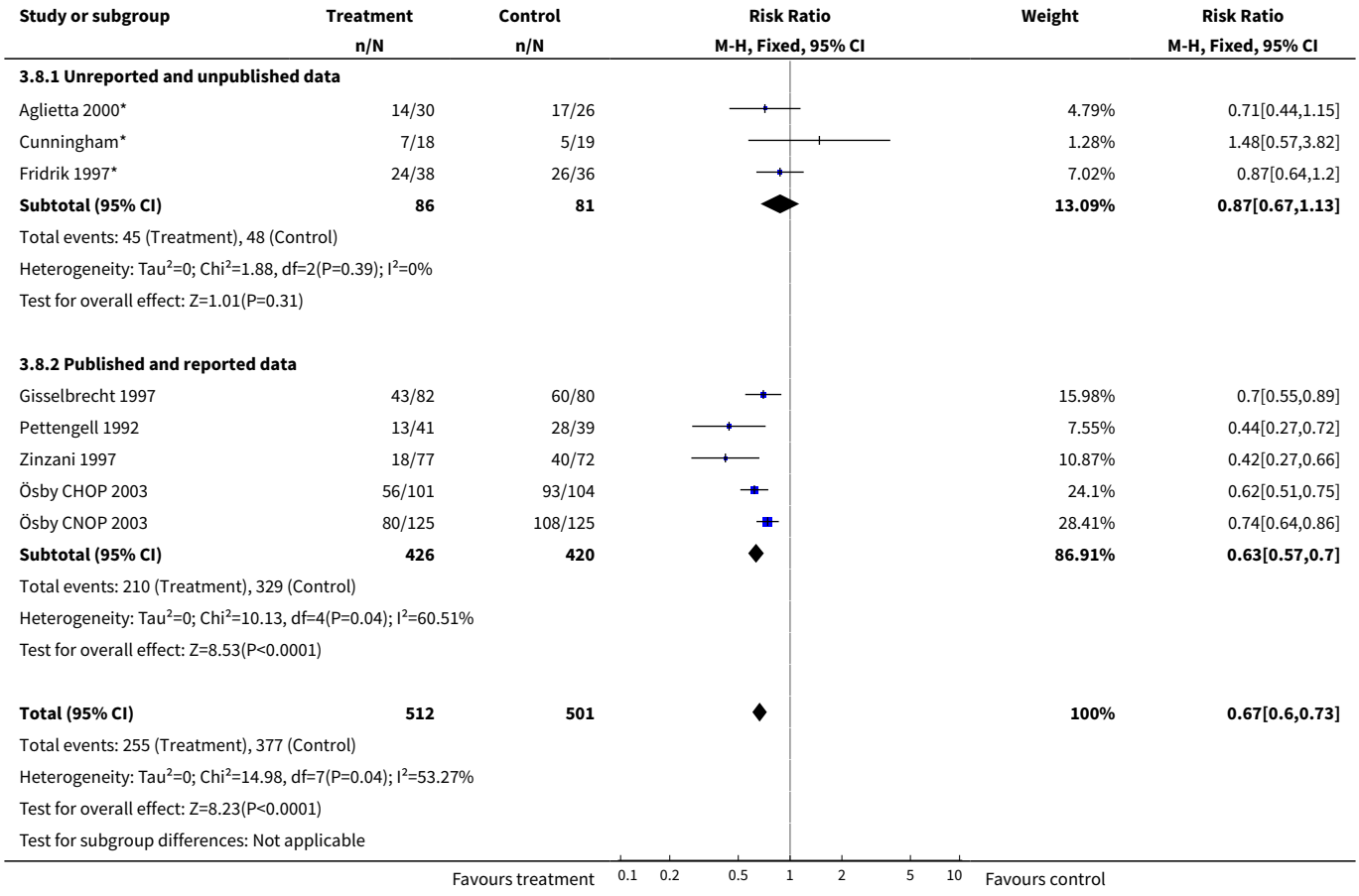
Analysis 3.7. Comparison 3 Sensitivity analysis: Neutropenia, Outcome 7 Concealed versus unclear method of allocation.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.7.1 Allocation concealed					
Aglietta 2000*	14/30	17/26		4.79%	0.71[0.44,1.15]
Cunningham*	7/18	5/19		1.28%	1.48[0.57,3.82]
Fridrik 1997*	24/38	26/36		7.02%	0.87[0.64,1.2]
Gisselbrecht 1997	43/82	60/80		15.98%	0.7[0.55,0.89]
Zinzani 1997	18/77	40/72		10.87%	0.42[0.27,0.66]
Ösby CHOP 2003	56/101	93/104		24.1%	0.62[0.51,0.75]
Ösby CNOP 2003	80/125	108/125		28.41%	0.74[0.64,0.86]
Subtotal (95% CI)	**471**	**462**		**92.45%**	**0.68[0.62,0.75]**
Total events: 242 (Treatment), 349 (Control)					
Heterogeneity: Tau^2=0; Chi^2=11.49, df=6(P=0.07); I^2=47.76%					
Test for overall effect: Z=7.57(P<0.0001)					
3.7.2 Method of allocation unclear					
Pettengell 1992	13/41	28/39		7.55%	0.44[0.27,0.72]



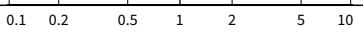


Analysis 3.8. Comparison 3 Sensitivity analysis: Neutropenia, Outcome 8 Published and reported data versus unpublished or unreported data.



Analysis 3.9. Comparison 3 Sensitivity analysis: Neutropenia, Outcome 9 Size of study.

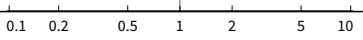
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.9.1 Study size <100 patients					
Aglietta 2000*	14/30	17/26		4.79%	0.71[0.44,1.15]
Cunningham*	7/18	5/19		1.28%	1.48[0.57,3.82]
Fridrik 1997*	24/38	26/36		7.02%	0.87[0.64,1.2]
Pettengell 1992	13/41	28/39		7.55%	0.44[0.27,0.72]
Subtotal (95% CI)	**127**	**120**		**20.64%**	**0.72[0.57,0.9]**
Total events: 58 (Treatment), 76 (Control)					
Heterogeneity: Tau^2=0; Chi^2=7.5, df=3(P=0.06); I^2=60%					
Test for overall effect: Z=2.84(P=0)					
3.9.2 Study size > 100 patients					
Gisselbrecht 1997	43/82	60/80		15.98%	0.7[0.55,0.89]
Zinzani 1997	18/77	40/72		10.87%	0.42[0.27,0.66]
Ösby CHOP 2003	56/101	93/104		24.1%	0.62[0.51,0.75]
Ösby CNOP 2003	80/125	108/125		28.41%	0.74[0.64,0.86]
Subtotal (95% CI)	**385**	**381**		**79.36%**	**0.65[0.59,0.73]**
Total events: 197 (Treatment), 301 (Control)					
Heterogeneity: Tau^2=0; Chi^2=7, df=3(P=0.07); I^2=57.17%					
Test for overall effect: Z=7.88(P<0.0001)					
Total (95% CI)	**512**	**501**		**100%**	**0.67[0.6,0.73]**
Total events: 255 (Treatment), 377 (Control)					
Heterogeneity: Tau^2=0; Chi^2=14.98, df=7(P=0.04); I^2=53.27%					
Test for overall effect: Z=8.23(P<0.0001)					
Test for subgroup differences: Not applicable					



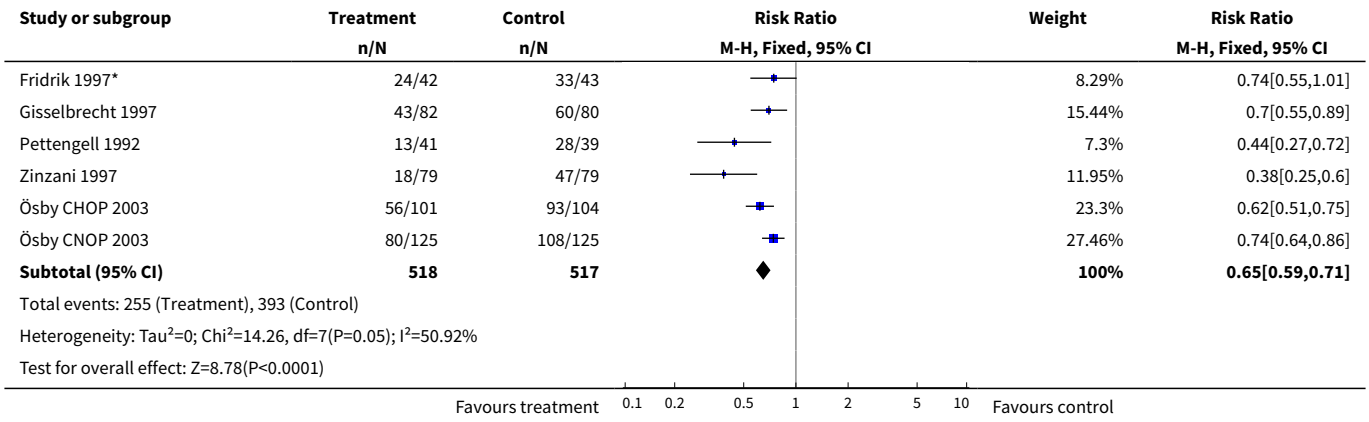
Favours treatment — Favours control

Analysis 3.10. Comparison 3 Sensitivity analysis: Neutropenia, Outcome 10 Worst case-best case.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.10.1 Worst case					
Aglietta 2000*	14/30	17/26		4.82%	0.71[0.44,1.15]
Cunningham*	7/18	5/21		1.22%	1.63[0.63,4.26]
Fridrik 1997*	28/42	26/43		6.8%	1.1[0.8,1.52]
Gisselbrecht 1997	43/82	60/80		16.09%	0.7[0.55,0.89]
Pettengell 1992	13/41	28/39		7.6%	0.44[0.27,0.72]
Zinzani 1997	19/79	40/79		10.59%	0.48[0.3,0.74]
Ösby CHOP 2003	56/101	93/104		24.27%	0.62[0.51,0.75]
Ösby CNOP 2003	80/125	108/125		28.6%	0.74[0.64,0.86]
Subtotal (95% CI)	**518**	**517**		**100%**	**0.69[0.62,0.76]**
Total events: 260 (Treatment), 377 (Control)					
Heterogeneity: Tau^2=0; Chi^2=19.26, df=7(P=0.01); I^2=63.65%					
Test for overall effect: Z=7.54(P<0.0001)					
3.10.2 Best case					
Aglietta 2000*	14/30	17/26		4.63%	0.71[0.44,1.15]
Cunningham*	7/18	7/21		1.64%	1.17[0.5,2.7]



Favours treatment — Favours control



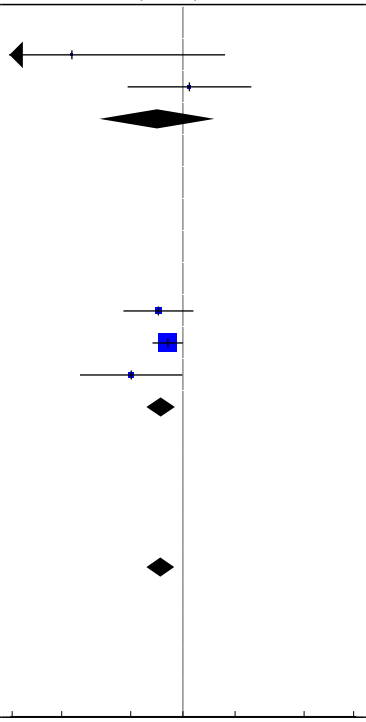
Comparison 4. Sensitivity analysis: Febrile Neutropenia

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 HD versus NHL	5	360	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.62, 0.89]
1.1 Hodgkin's disease	2	44	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.33, 1.52]
1.2 Non-Hodgkin's lymphoma	3	316	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.62, 0.90]
2 Use of antibiotic prophylaxis	5	360	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.62, 0.89]
2.1 No antibiotic prophylaxis given	4	280	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.65, 0.95]
2.2 Antibiotic prophylaxis given	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.26, 0.99]
3 Blinded versus open label studies	5	360	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.62, 0.89]
3.1 placebo controlled studies	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.26, 0.99]
3.2 open label studies	4	280	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.65, 0.95]
4 Concealed versus unclear method of allo-cation	5	360	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.62, 0.89]
4.1 allocation concealed	4	280	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.65, 0.95]
4.2 method of allocation unclear	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.26, 0.99]
5 Size of study	5		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
5.1 Study size <100 patients	4	198	Risk Ratio (IV, Fixed, 95% CI)	0.68 [0.49, 0.96]
5.2 Study size >100 patients	1	162	Risk Ratio (IV, Fixed, 95% CI)	0.82 [0.67, 1.00]
6 Worst case-best case	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Worst case	5	380	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.69, 0.99]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
6.2 Best case	5	380	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.57, 0.82]

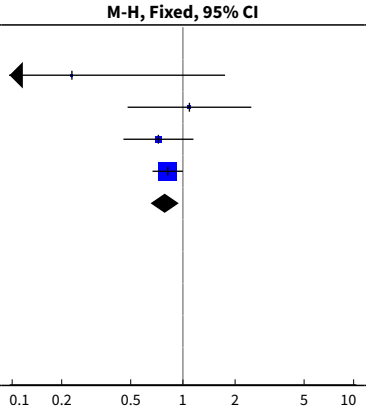
Analysis 4.1. Comparison 4 Sensitivity analysis: Febrile Neutropenia, Outcome 1 HD versus NHL.

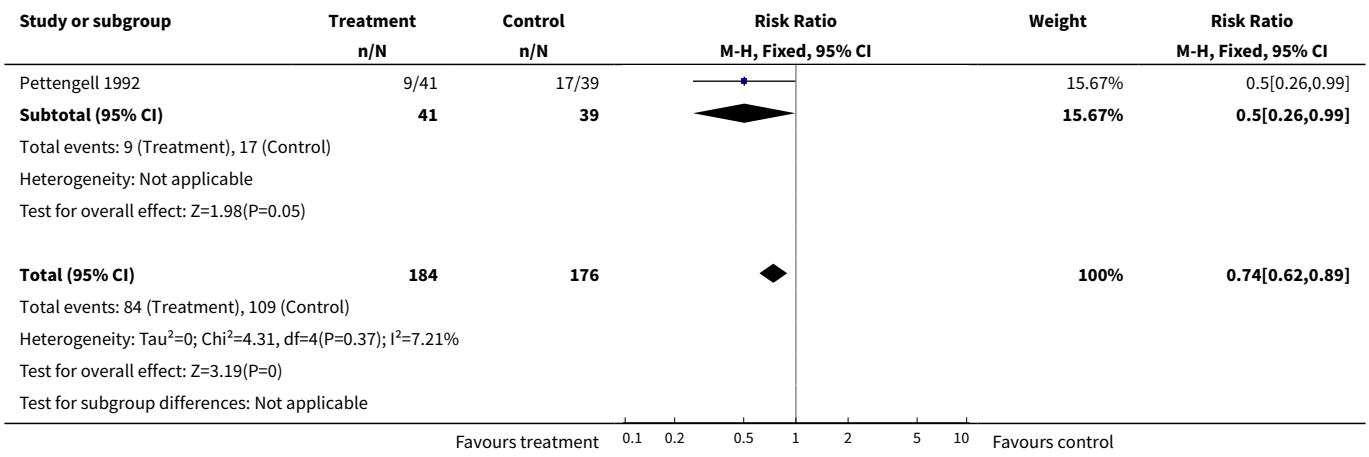
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.1.1 Hodgkin's disease					
Dunlop MOPP 1998	1/12	4/11		3.75%	0.23[0.03,1.75]
Dunlop MOPP/EVAP 98	6/11	5/10		4.71%	1.09[0.48,2.48]
Subtotal (95% CI)	**23**	**21**		**8.47%**	**0.71[0.33,1.52]**
Total events: 7 (Treatment), 9 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.24, df=1(P=0.13); I^2=55.42%					
Test for overall effect: Z=0.88(P=0.38)					
4.1.2 Non-Hodgkin's lymphoma					
Fridrik 1997	16/38	21/36		19.4%	0.72[0.45,1.15]
Gisselbrecht 1997	52/82	62/80		56.46%	0.82[0.67,1]
Pettengell 1992	9/41	17/39		15.67%	0.5[0.26,0.99]
Subtotal (95% CI)	**161**	**155**		**91.53%**	**0.74[0.62,0.9]**
Total events: 77 (Treatment), 100 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.14, df=2(P=0.34); I^2=6.38%					
Test for overall effect: Z=3.07(P=0)					
Total (95% CI)	**184**	**176**		**100%**	**0.74[0.62,0.89]**
Total events: 84 (Treatment), 109 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.31, df=4(P=0.37); I^2=7.21%					
Test for overall effect: Z=3.19(P=0)					
Test for subgroup differences: Not applicable					



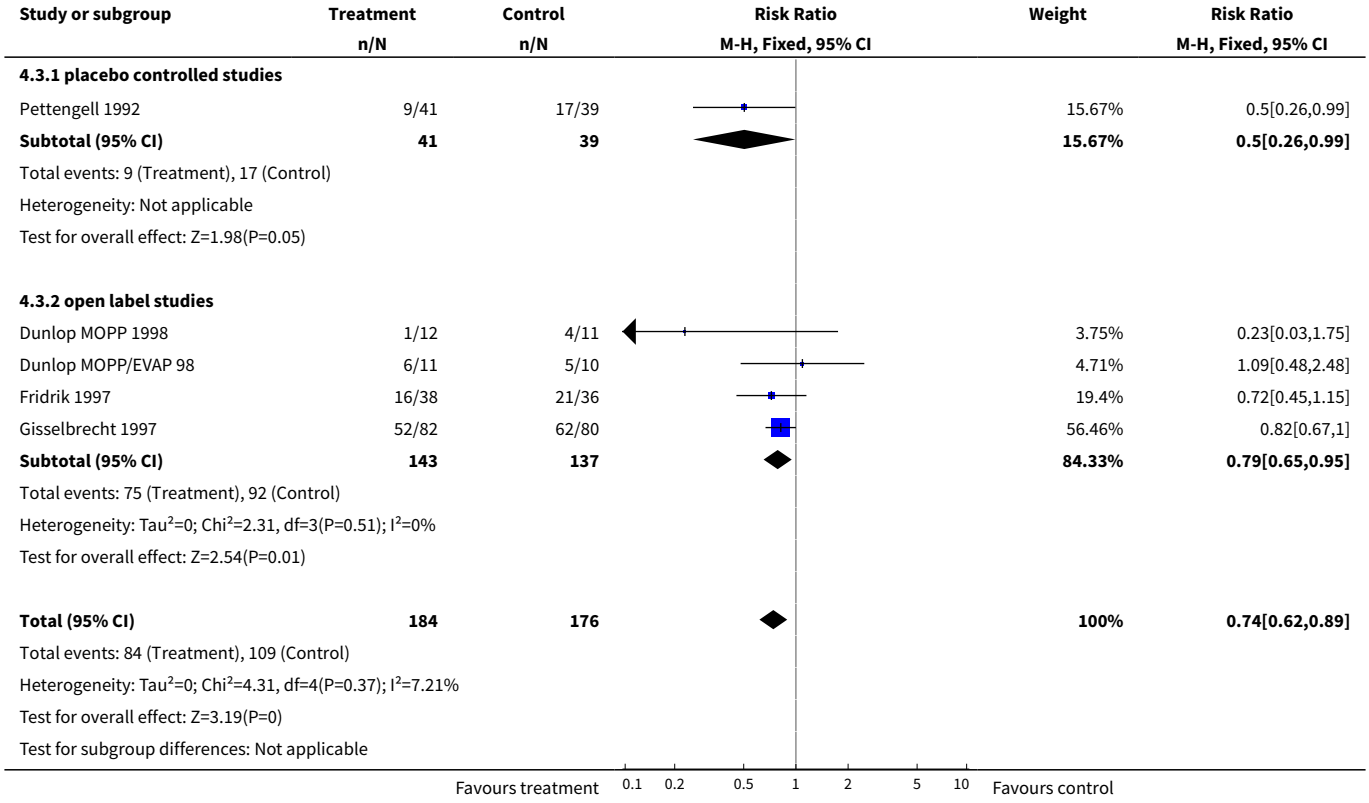
Analysis 4.2. Comparison 4 Sensitivity analysis: Febrile Neutropenia, Outcome 2 Use of antibiotic prophylaxis.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.2.1 No antibiotic prophylaxis given					
Dunlop MOPP 1998	1/12	4/11		3.75%	0.23[0.03,1.75]
Dunlop MOPP/EVAP 98	6/11	5/10		4.71%	1.09[0.48,2.48]
Fridrik 1997	16/38	21/36		19.4%	0.72[0.45,1.15]
Gisselbrecht 1997	52/82	62/80		56.46%	0.82[0.67,1]
Subtotal (95% CI)	**143**	**137**		**84.33%**	**0.79[0.65,0.95]**
Total events: 75 (Treatment), 92 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.31, df=3(P=0.51); I^2=0%					
Test for overall effect: Z=2.54(P=0.01)					
4.2.2 Antibiotic prophylaxis given					

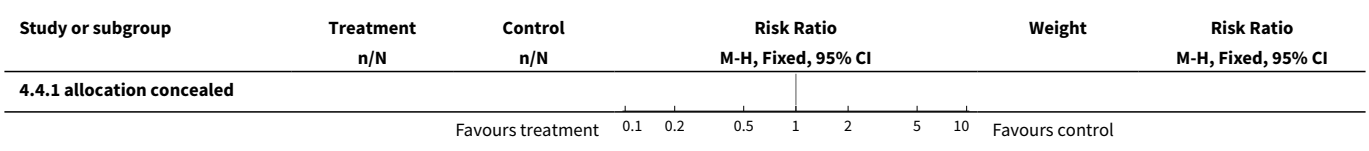


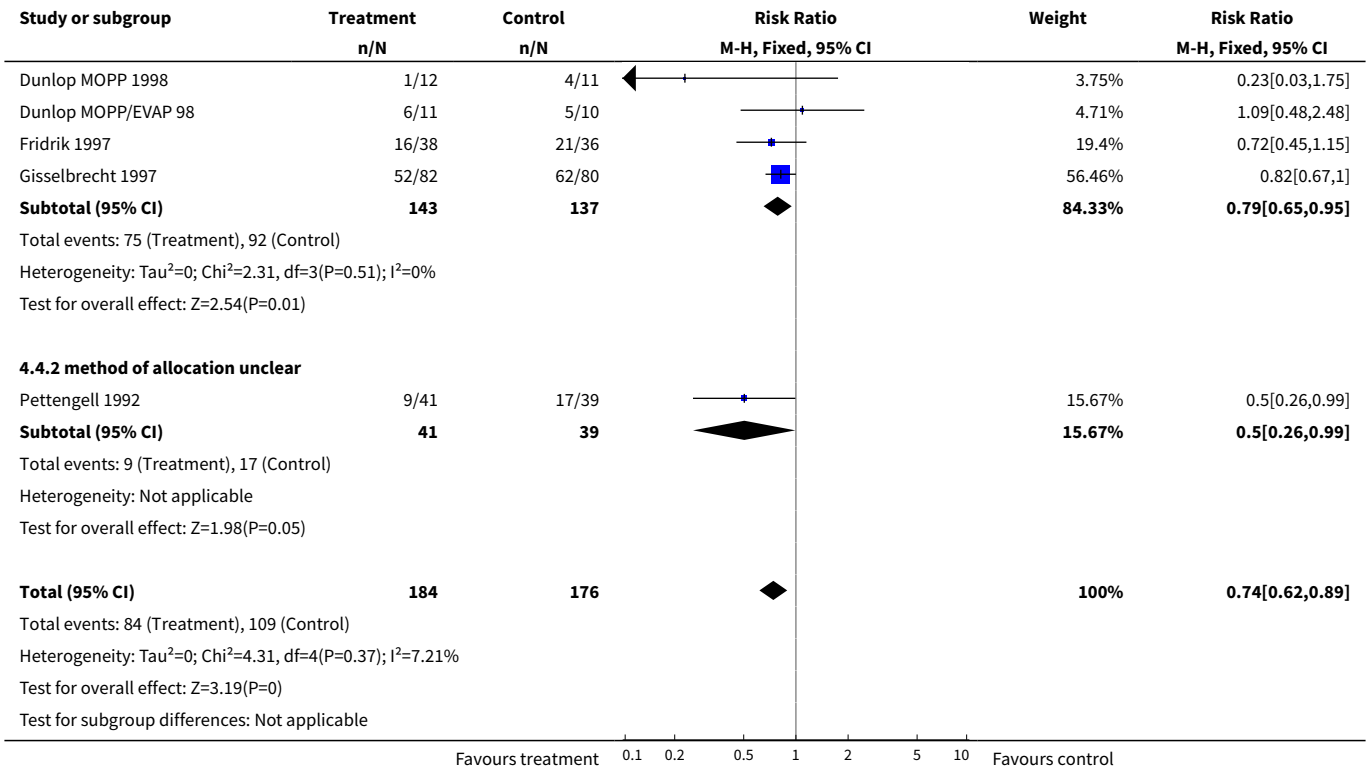


Analysis 4.3. Comparison 4 Sensitivity analysis: Febrile Neutropenia, Outcome 3 Blinded versus open label studies.



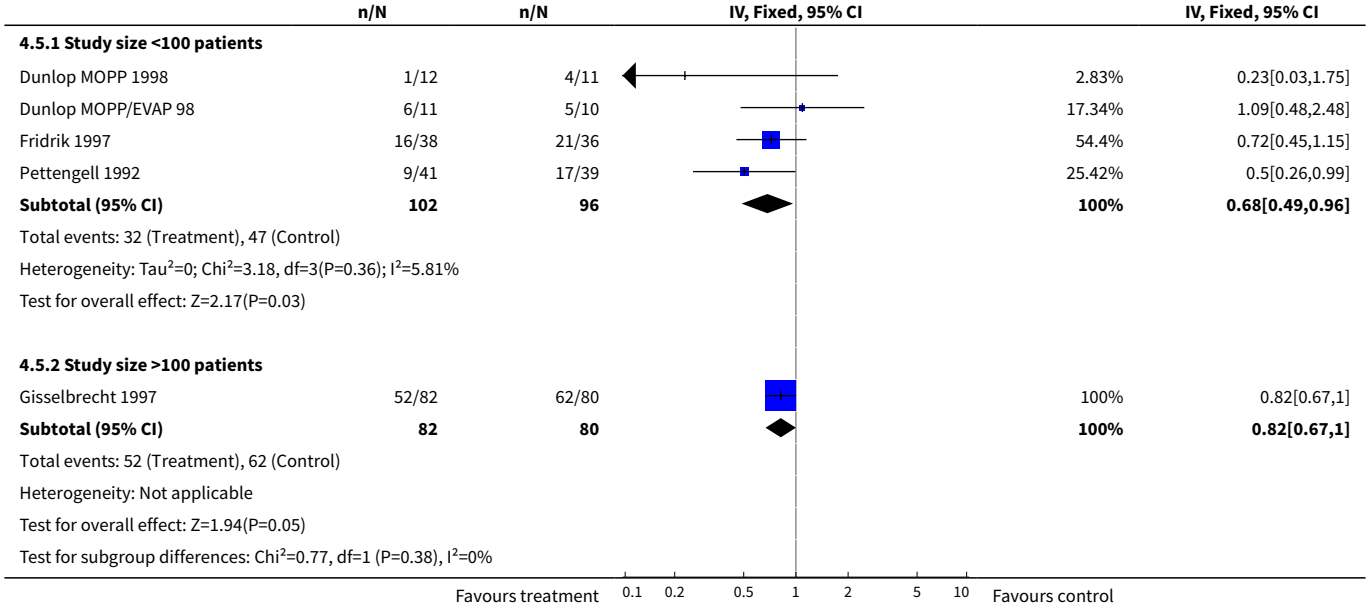
Analysis 4.4. Comparison 4 Sensitivity analysis: Febrile Neutropenia, Outcome 4 Concealed versus unclear method of allocation.





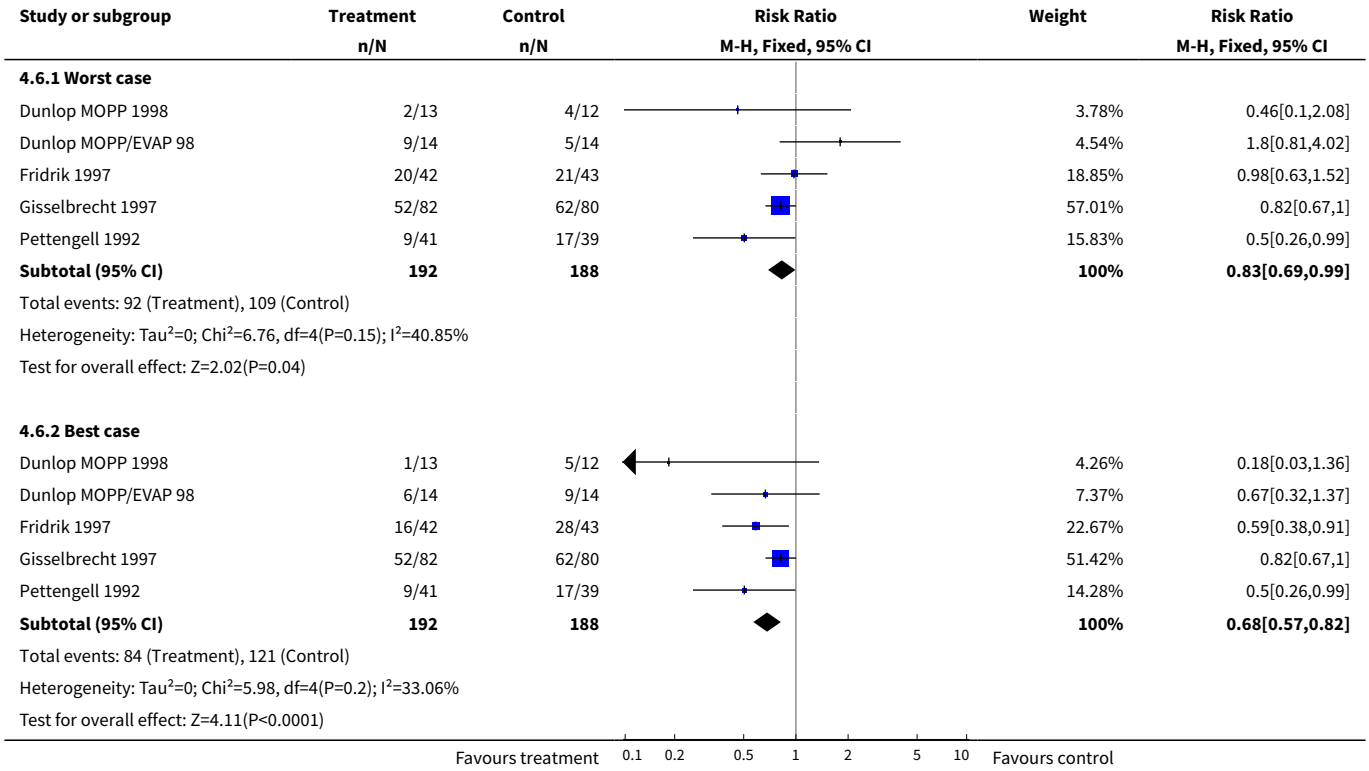
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dunlop MOPP 1998	1/12	4/11		3.75%	0.23[0.03,1.75]
Dunlop MOPP/EVAP 98	6/11	5/10		4.71%	1.09[0.48,2.48]
Fridrik 1997	16/38	21/36		19.4%	0.72[0.45,1.15]
Gisselbrecht 1997	52/82	62/80		56.46%	0.82[0.67,1]
Subtotal (95% CI)	**143**	**137**		**84.33%**	**0.79[0.65,0.95]**
Total events: 75 (Treatment), 92 (Control)					
Heterogeneity: Tau²=0; Chi²=2.31, df=3(P=0.51); I²=0%					
Test for overall effect: Z=2.54(P=0.01)					
4.4.2 method of allocation unclear					
Pettengell 1992	9/41	17/39		15.67%	0.5[0.26,0.99]
Subtotal (95% CI)	**41**	**39**		**15.67%**	**0.5[0.26,0.99]**
Total events: 9 (Treatment), 17 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.98(P=0.05)					
Total (95% CI)	**184**	**176**		**100%**	**0.74[0.62,0.89]**
Total events: 84 (Treatment), 109 (Control)					
Heterogeneity: Tau²=0; Chi²=4.31, df=4(P=0.37); I²=7.21%					
Test for overall effect: Z=3.19(P=0)					
Test for subgroup differences: Not applicable					

Analysis 4.5. Comparison 4 Sensitivity analysis: Febrile Neutropenia, Outcome 5 Size of study.



Study or subgroup	Treatment n/N	Control n/N	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
4.5.1 Study size <100 patients					
Dunlop MOPP 1998	1/12	4/11		2.83%	0.23[0.03,1.75]
Dunlop MOPP/EVAP 98	6/11	5/10		17.34%	1.09[0.48,2.48]
Fridrik 1997	16/38	21/36		54.4%	0.72[0.45,1.15]
Pettengell 1992	9/41	17/39		25.42%	0.5[0.26,0.99]
Subtotal (95% CI)	**102**	**96**		**100%**	**0.68[0.49,0.96]**
Total events: 32 (Treatment), 47 (Control)					
Heterogeneity: Tau²=0; Chi²=3.18, df=3(P=0.36); I²=5.81%					
Test for overall effect: Z=2.17(P=0.03)					
4.5.2 Study size >100 patients					
Gisselbrecht 1997	52/82	62/80		100%	0.82[0.67,1]
Subtotal (95% CI)	**82**	**80**		**100%**	**0.82[0.67,1]**
Total events: 52 (Treatment), 62 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.94(P=0.05)					
Test for subgroup differences: Chi²=0.77, df=1 (P=0.38), I²=0%					

Analysis 4.6. Comparison 4 Sensitivity analysis: Febrile Neutropenia, Outcome 6 Worst case-best case.

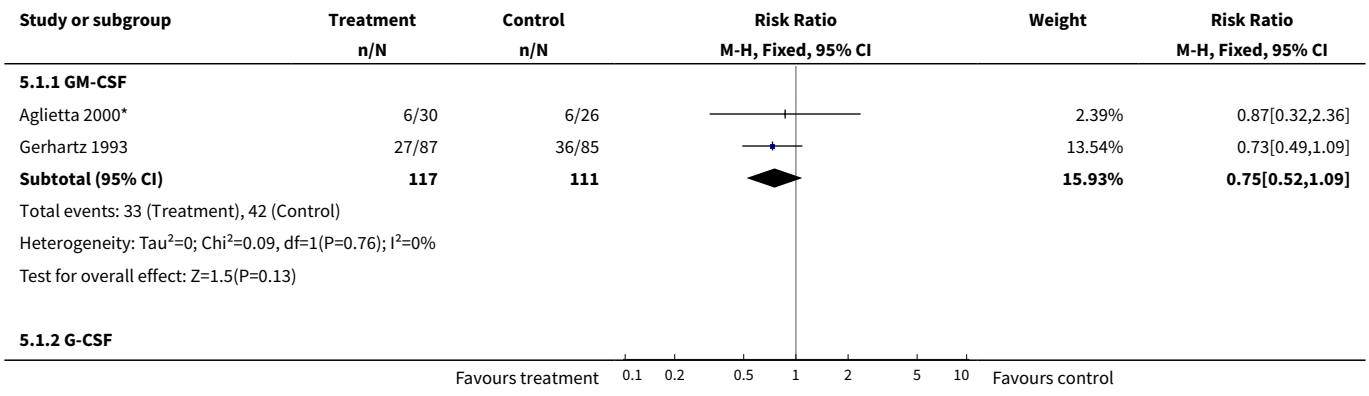


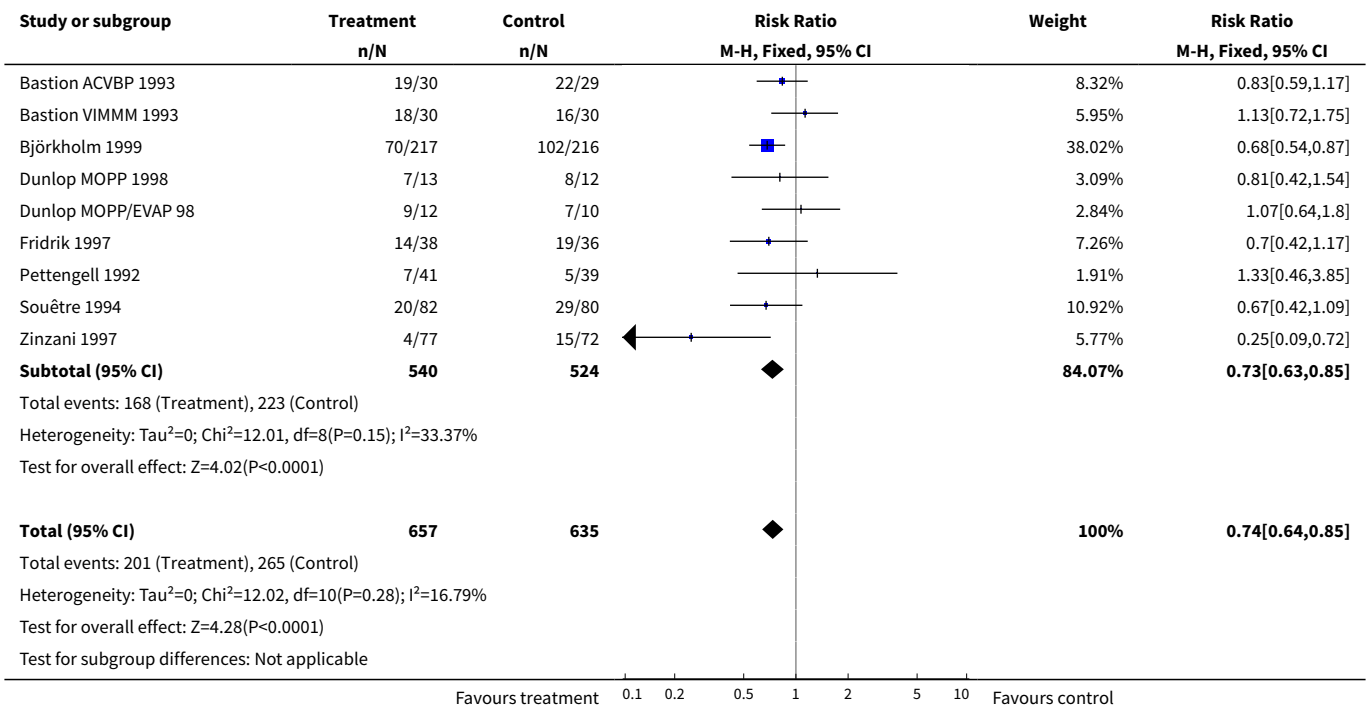
Comparison 5. Sensitivity analysis: Infection

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 G-CSF versus GM-CSF	11	1292	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.64, 0.85]
1.1 GM-CSF	2	228	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.52, 1.09]
1.2 G-CSF	9	1064	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.63, 0.85]
2 HD versus NHL	11	1292	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.64, 0.85]
2.1 Hodgkin's disease	3	103	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.61, 1.37]
2.2 Non-Hodgkin's lymphoma	8	1189	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.62, 0.84]
3 Age	11	1292	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.64, 0.85]
3.1 Adults, all ages	9	710	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.69, 0.98]
3.2 Adults, age older 60	2	582	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.50, 0.79]
4 Use of antibiotic prophylaxis	11	1292	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.64, 0.85]
4.1 No antibiotic prophylaxis given	9	1063	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.65, 0.87]

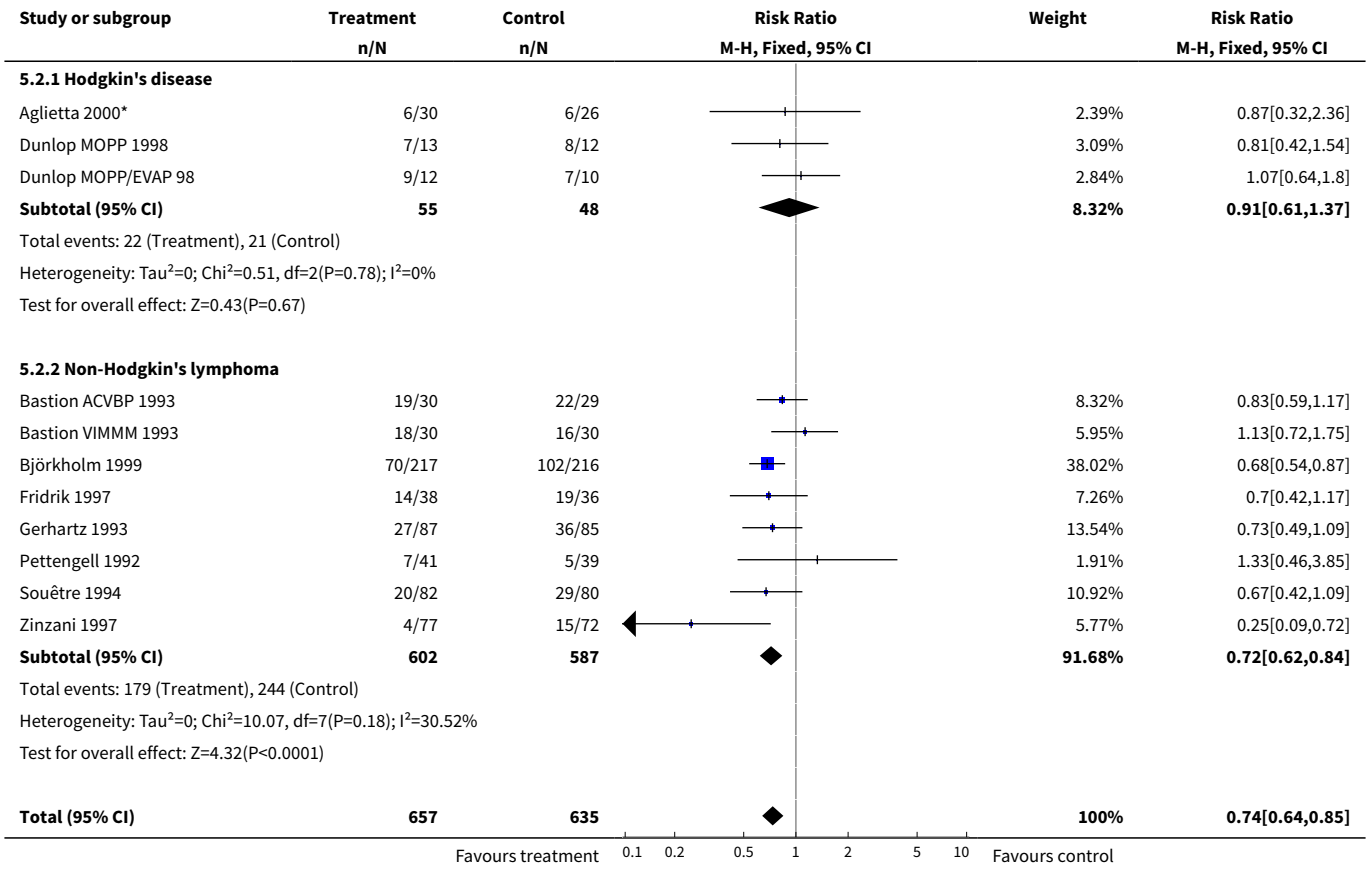
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2 Antbiobiotic prophylaxis given	2	229	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.26, 1.04]
5 Blinded versus open label studies	11	1292	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.64, 0.85]
5.1 Placebo controlled studies	5	509	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.65, 0.99]
5.2 Open label studies	6	783	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.57, 0.83]
6 Concealed versus unclear method of allocation	11	1292	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.64, 0.85]
6.1 Allocation concealed	8	1093	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.58, 0.80]
6.2 Method of allocation unclear	3	199	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.76, 1.32]
7 Published and reported data versus unpublished, unreported or abstract publications only	11	1292	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.64, 0.85]
7.1 Unreported, unpublished or abstract publicated data	4	608	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.64, 0.91]
7.2 Peer-reviewed data	7	684	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.56, 0.88]
8 Size of study	11	1292	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.64, 0.85]
8.1 Study size <100 patients	5	257	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.64, 1.19]
8.2 Study size >100 patients	6	1035	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.60, 0.83]
9 Worst case-best case	11		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 Worst case	11	1350	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.73, 0.96]
9.2 Best case	11	1350	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.58, 0.76]

Analysis 5.1. Comparison 5 Sensitivity analysis: Infection, Outcome 1 G-CSF versus GM-CSF.





Analysis 5.2. Comparison 5 Sensitivity analysis: Infection, Outcome 2 HD versus NHL.



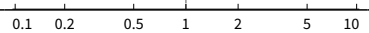
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Total events: 201 (Treatment), 265 (Control)					
Heterogeneity: Tau²=0; Chi²=12.02, df=10(P=0.28); I²=16.79%					
Test for overall effect: Z=4.28(P<0.0001)					
Test for subgroup differences: Not applicable					

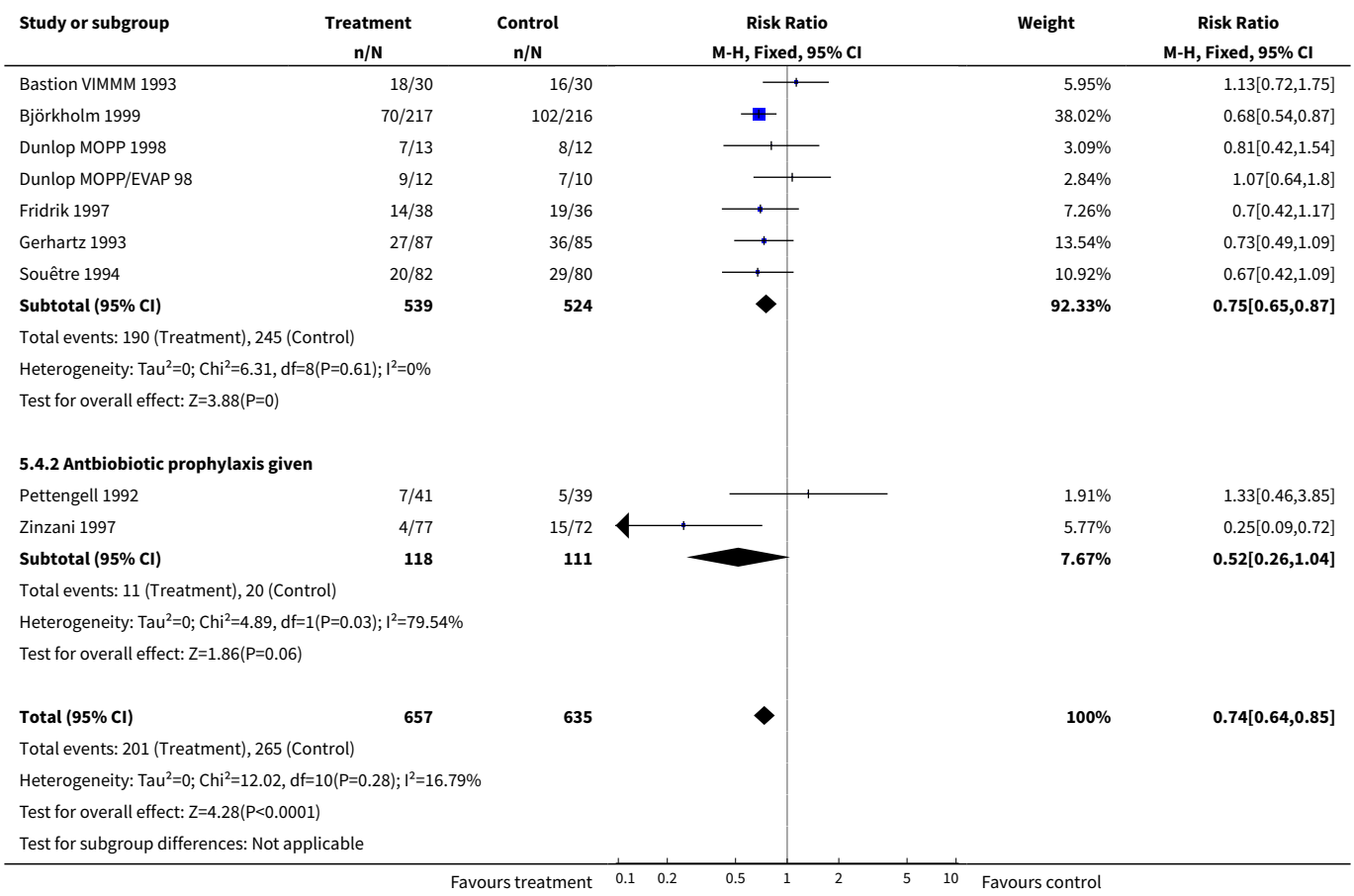
Analysis 5.3. Comparison 5 Sensitivity analysis: Infection, Outcome 3 Age.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
5.3.1 Adults, all ages					
Aglietta 2000*	6/30	6/26		2.39%	0.87[0.32,2.36]
Bastion ACVBP 1993	19/30	22/29		8.32%	0.83[0.59,1.17]
Bastion VIMMM 1993	18/30	16/30		5.95%	1.13[0.72,1.75]
Dunlop MOPP 1998	7/13	8/12		3.09%	0.81[0.42,1.54]
Dunlop MOPP/EVAP 98	9/12	7/10		2.84%	1.07[0.64,1.8]
Fridrik 1997	14/38	19/36		7.26%	0.7[0.42,1.17]
Gerhartz 1993	27/87	36/85		13.54%	0.73[0.49,1.09]
Pettengell 1992	7/41	5/39		1.91%	1.33[0.46,3.85]
Souêtre 1994	20/82	29/80		10.92%	0.67[0.42,1.09]
Subtotal (95% CI)	**363**	**347**		**56.22%**	**0.82[0.69,0.98]**
Total events: 127 (Treatment), 148 (Control)					
Heterogeneity: Tau²=0; Chi²=5.11, df=8(P=0.75); I²=0%					
Test for overall effect: Z=2.2(P=0.03)					
5.3.2 Adults, age older 60					
Björkholm 1999	70/217	102/216		38.02%	0.68[0.54,0.87]
Zinzani 1997	4/77	15/72		5.77%	0.25[0.09,0.72]
Subtotal (95% CI)	**294**	**288**		**43.78%**	**0.63[0.5,0.79]**
Total events: 74 (Treatment), 117 (Control)					
Heterogeneity: Tau²=0; Chi²=3.44, df=1(P=0.06); I²=70.91%					
Test for overall effect: Z=3.93(P<0.0001)					
Total (95% CI)	**657**	**635**		**100%**	**0.74[0.64,0.85]**
Total events: 201 (Treatment), 265 (Control)					
Heterogeneity: Tau²=0; Chi²=12.02, df=10(P=0.28); I²=16.79%					
Test for overall effect: Z=4.28(P<0.0001)					
Test for subgroup differences: Not applicable					

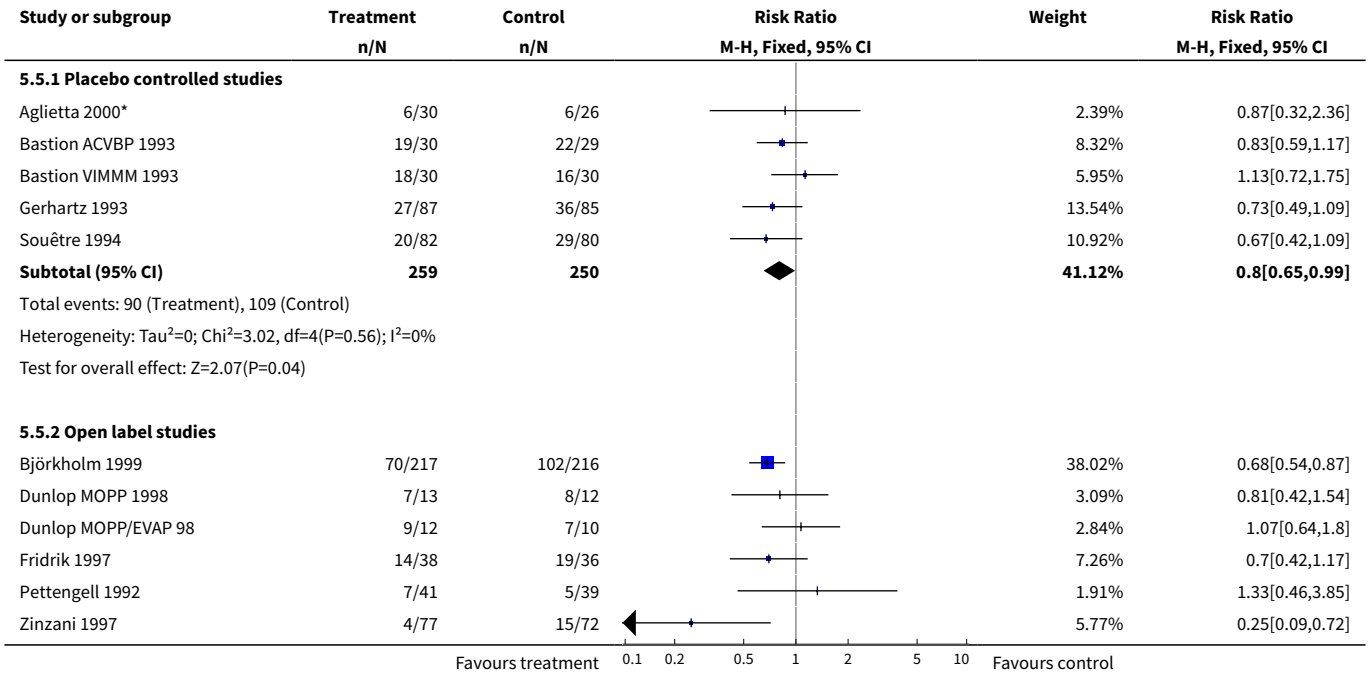
Analysis 5.4. Comparison 5 Sensitivity analysis: Infection, Outcome 4 Use of antibiotic prophylaxis.

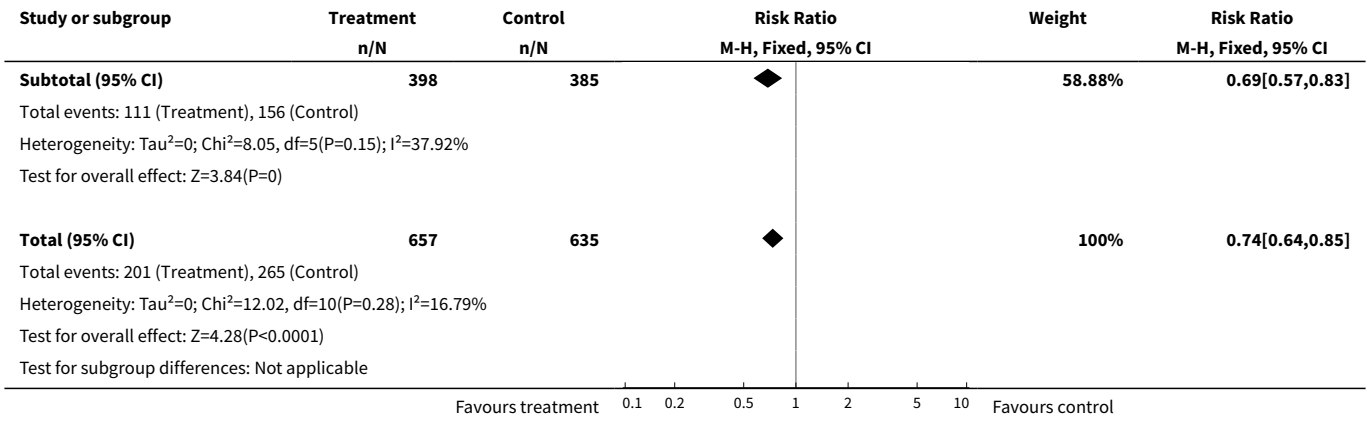
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
5.4.1 No antibiotic prophylaxis given					
Aglietta 2000*	6/30	6/26		2.39%	0.87[0.32,2.36]
Bastion ACVBP 1993	19/30	22/29		8.32%	0.83[0.59,1.17]



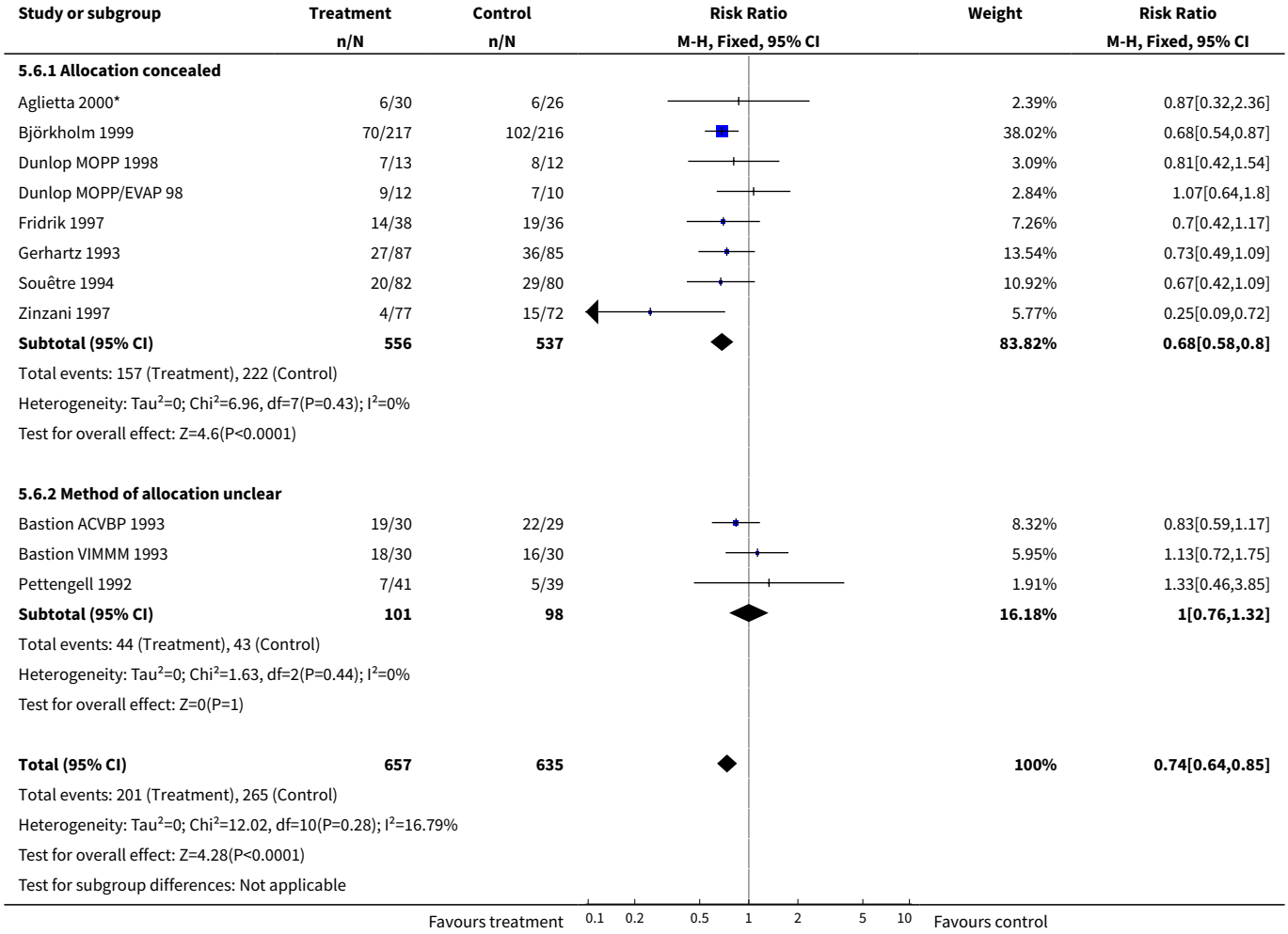


Analysis 5.5. Comparison 5 Sensitivity analysis: Infection, Outcome 5 Blinded versus open label studies.



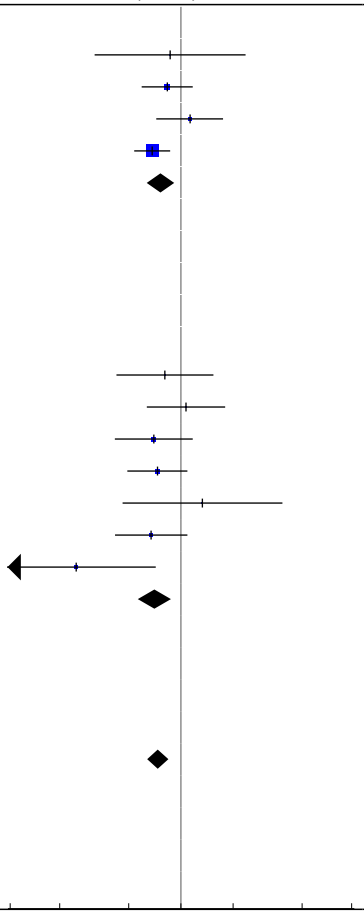


Analysis 5.6. Comparison 5 Sensitivity analysis: Infection, Outcome 6 Concealed versus unclear method of allocation.



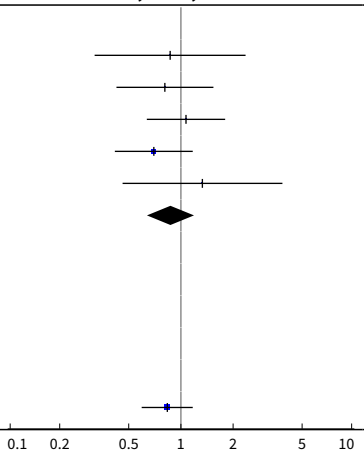
Analysis 5.7. Comparison 5 Sensitivity analysis: Infection, Outcome 7 Published and reported data versus unpublished, unreported or abstract publications only.

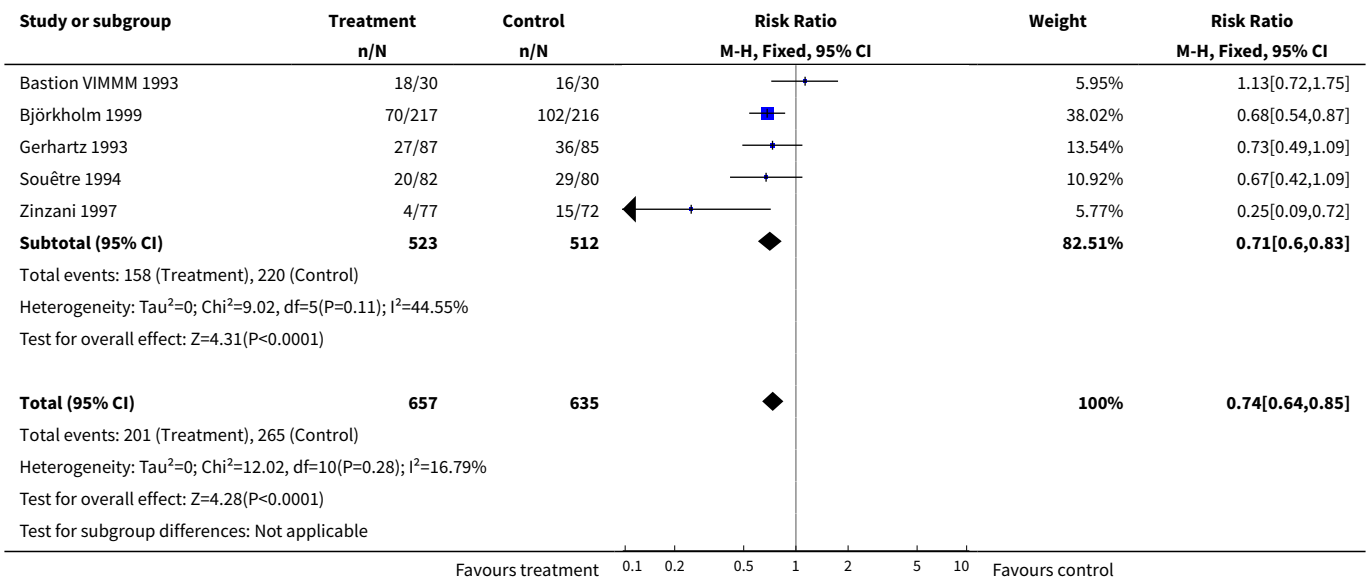
Study or subgroup	G-/GM-CSF n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
5.7.1 Unreported, unpublished or abstract publicated data					
Aglietta 2000*	6/30	6/26		2.39%	0.87[0.32,2.36]
Bastion ACVBP 1993	19/30	22/29		8.32%	0.83[0.59,1.17]
Bastion VIMMM 1993	18/30	16/30		5.95%	1.13[0.72,1.75]
Björkholm 1999	70/217	102/216		38.02%	0.68[0.54,0.87]
Subtotal (95% CI)	**307**	**301**		**54.68%**	**0.76[0.64,0.91]**
Total events: 113 (G-/GM-CSF), 146 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.09, df=3(P=0.25); I^2=26.71%					
Test for overall effect: Z=2.92(P=0)					
5.7.2 Peer-reviewed data					
Dunlop MOPP 1998	7/13	8/12		3.09%	0.81[0.42,1.54]
Dunlop MOPP/EVAP 98	9/12	7/10		2.84%	1.07[0.64,1.8]
Fridrik 1997	14/38	19/36		7.26%	0.7[0.42,1.17]
Gerhartz 1993	27/87	36/85		13.54%	0.73[0.49,1.09]
Pettengell 1992	7/41	5/39		1.91%	1.33[0.46,3.85]
Souêtre 1994	20/82	29/80		10.92%	0.67[0.42,1.09]
Zinzani 1997	4/77	15/72		5.77%	0.25[0.09,0.72]
Subtotal (95% CI)	**350**	**334**		**45.32%**	**0.7[0.56,0.88]**
Total events: 88 (G-/GM-CSF), 119 (Control)					
Heterogeneity: Tau^2=0; Chi^2=7.87, df=6(P=0.25); I^2=23.78%					
Test for overall effect: Z=3.14(P=0)					
Total (95% CI)	**657**	**635**		**100%**	**0.74[0.64,0.85]**
Total events: 201 (G-/GM-CSF), 265 (Control)					
Heterogeneity: Tau^2=0; Chi^2=12.02, df=10(P=0.28); I^2=16.79%					
Test for overall effect: Z=4.28(P<0.0001)					
Test for subgroup differences: Not applicable					



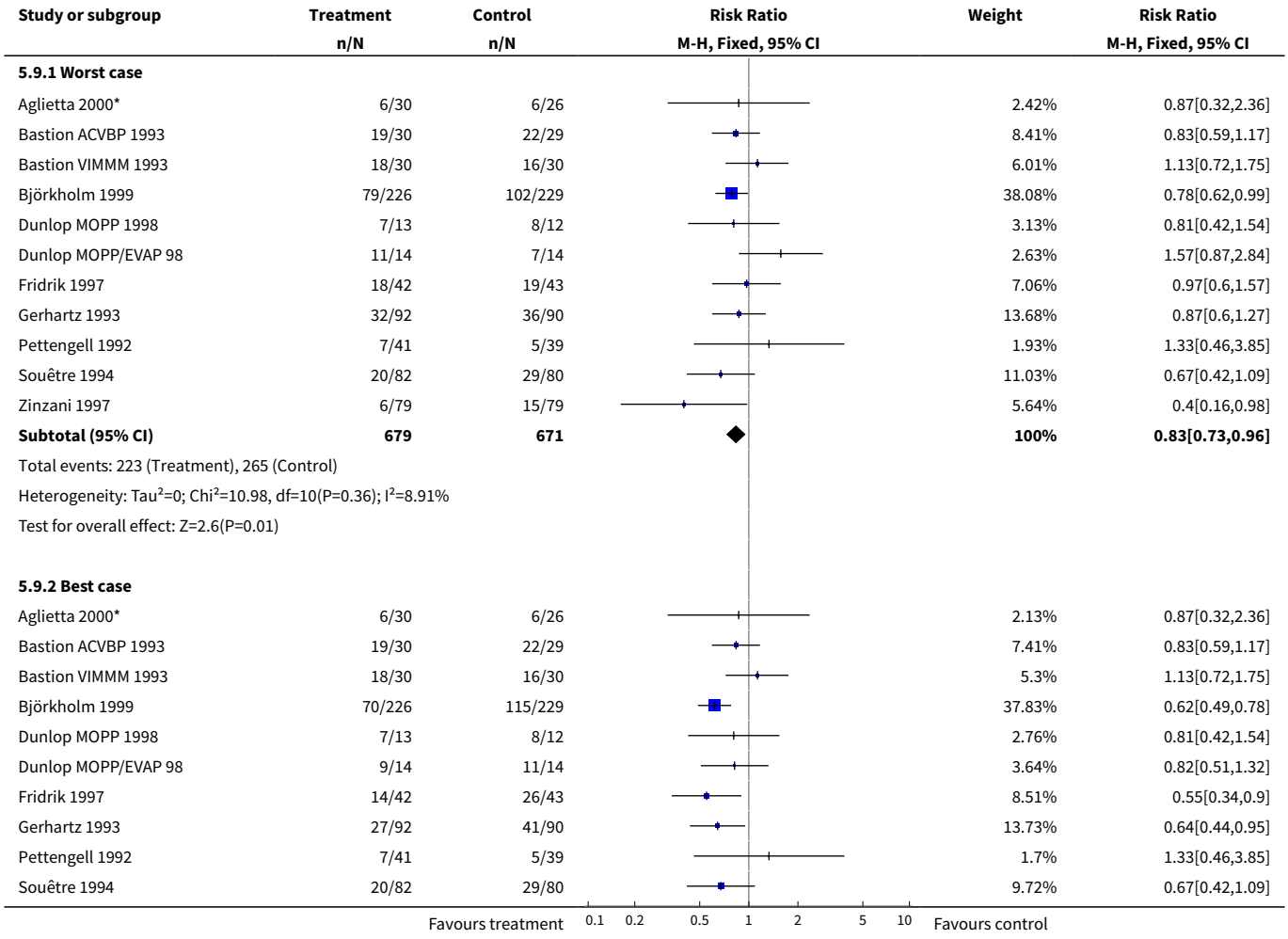
Analysis 5.8. Comparison 5 Sensitivity analysis: Infection, Outcome 8 Size of study.

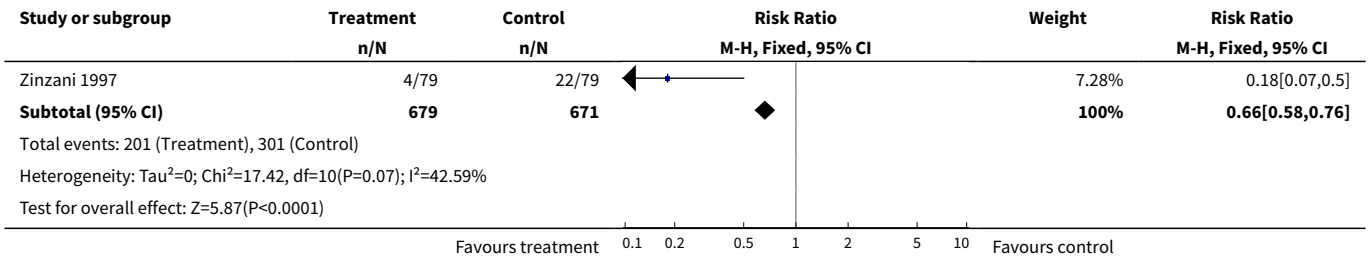
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
5.8.1 Study size <100 patients					
Aglietta 2000*	6/30	6/26		2.39%	0.87[0.32,2.36]
Dunlop MOPP 1998	7/13	8/12		3.09%	0.81[0.42,1.54]
Dunlop MOPP/EVAP 98	9/12	7/10		2.84%	1.07[0.64,1.8]
Fridrik 1997	14/38	19/36		7.26%	0.7[0.42,1.17]
Pettengell 1992	7/41	5/39		1.91%	1.33[0.46,3.85]
Subtotal (95% CI)	**134**	**123**		**17.49%**	**0.87[0.64,1.19]**
Total events: 43 (Treatment), 45 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.98, df=4(P=0.74); I^2=0%					
Test for overall effect: Z=0.87(P=0.38)					
5.8.2 Study size >100 patients					
Bastion ACVBP 1993	19/30	22/29		8.32%	0.83[0.59,1.17]





Analysis 5.9. Comparison 5 Sensitivity analysis: Infection, Outcome 9 Worst case-best case.





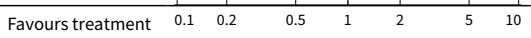
Comparison 6. Sensitivity analysis: Complete response

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 GM-CSF versus G-CSF	13	2368	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.95, 1.10]
1.1 GM-CSF	2	228	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.88, 1.31]
1.2 G-CSF	11	2140	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.94, 1.10]
2 HD versus NHL	13	2368	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.95, 1.10]
2.1 Hodgkin's disease	3	106	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.89, 1.72]
2.2 Non-Hodgkin's lymphoma	10	2262	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.94, 1.09]
3 Age	13	2368	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.95, 1.10]
3.1 Adults, all ages	8	591	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.98, 1.25]
3.2 Adults, age older 60	5	1777	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.91, 1.09]
4 Use of antibiotic prophylaxis	13	2368	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.95, 1.10]
4.1 No antibiotic prophylaxis given	11	1435	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.93, 1.11]
4.2 Antibiotic prophylaxis given	2	933	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.91, 1.17]
5 Blinded versus open label studies	13	2368	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.95, 1.10]
5.1 Placebo controlled studies	4	431	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.92, 1.20]
5.2 Open label studies	9	1937	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.94, 1.11]
6 Published and reported data versus unpublished or unreported data	13	2368	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.95, 1.10]
6.1 Data not published in a peer-review journal	3	89	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [0.88, 2.86]
6.2 Peer-reviewed data	10	2279	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.94, 1.09]
7 Size of studies	13	2368	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.95, 1.10]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
7.1 Study size n<100	6	258	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [1.08, 1.60]
7.2 Study size n>100	7	2110	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.92, 1.07]
8 Worst case - best case	15		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Best case	13	2405	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.98, 1.13]
8.2 Worst case	13	2405	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.93, 1.07]

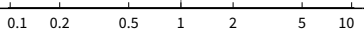
Analysis 6.1. Comparison 6 Sensitivity analysis: Complete response, Outcome 1 GM-CSF versus G-CSF.

Study or subgroup	Control n/N	G-/GM-CSF n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
6.1.1 GM-CSF					
Aglietta 2000	21/30	16/26		2.69%	1.14[0.78,1.67]
Engelhard 1994	56/87	52/85		8.24%	1.05[0.84,1.32]
Subtotal (95% CI)	**117**	**111**		**10.93%**	**1.07[0.88,1.31]**
Total events: 77 (Control), 68 (G-/GM-CSF)					
Heterogeneity: Tau^2=0; Chi^2=0.12, df=1(P=0.73); I^2=0%					
Test for overall effect: Z=0.7(P=0.48)					
6.1.2 G-CSF					
Avilés 1994	16/20	12/22		1.79%	1.47[0.94,2.28]
Burton 2006	201/387	199/397		30.78%	1.04[0.9,1.19]
Cunningham*	3/18	1/21		0.14%	3.5[0.4,30.77]
Doorduijn 2003	102/197	106/192		16.82%	0.94[0.78,1.13]
Dunlop MOPP 1998*	6/13	4/12		0.65%	1.38[0.51,3.74]
Dunlop MOPP/EVAP 98*	9/14	5/11		0.88%	1.41[0.66,3.01]
Fridrik 1997	29/35	24/36		3.71%	1.24[0.94,1.64]
Gisselbrecht 1997	54/81	57/80		8.99%	0.94[0.76,1.15]
Zinzani 1997	46/77	42/72		6.8%	1.02[0.78,1.34]
Ösby CHOP 2003	62/101	61/104		9.42%	1.05[0.84,1.31]
Ösby CNOP 2003	51/125	58/125		9.09%	0.88[0.66,1.17]
Subtotal (95% CI)	**1068**	**1072**		**89.07%**	**1.02[0.94,1.1]**
Total events: 579 (Control), 569 (G-/GM-CSF)					
Heterogeneity: Tau^2=0; Chi^2=9.52, df=10(P=0.48); I^2=0%					
Test for overall effect: Z=0.48(P=0.63)					
Total (95% CI)	**1185**	**1183**		**100%**	**1.03[0.95,1.1]**
Total events: 656 (Control), 637 (G-/GM-CSF)					
Heterogeneity: Tau^2=0; Chi^2=9.84, df=12(P=0.63); I^2=0%					
Test for overall effect: Z=0.67(P=0.5)					
Test for subgroup differences: Not applicable					



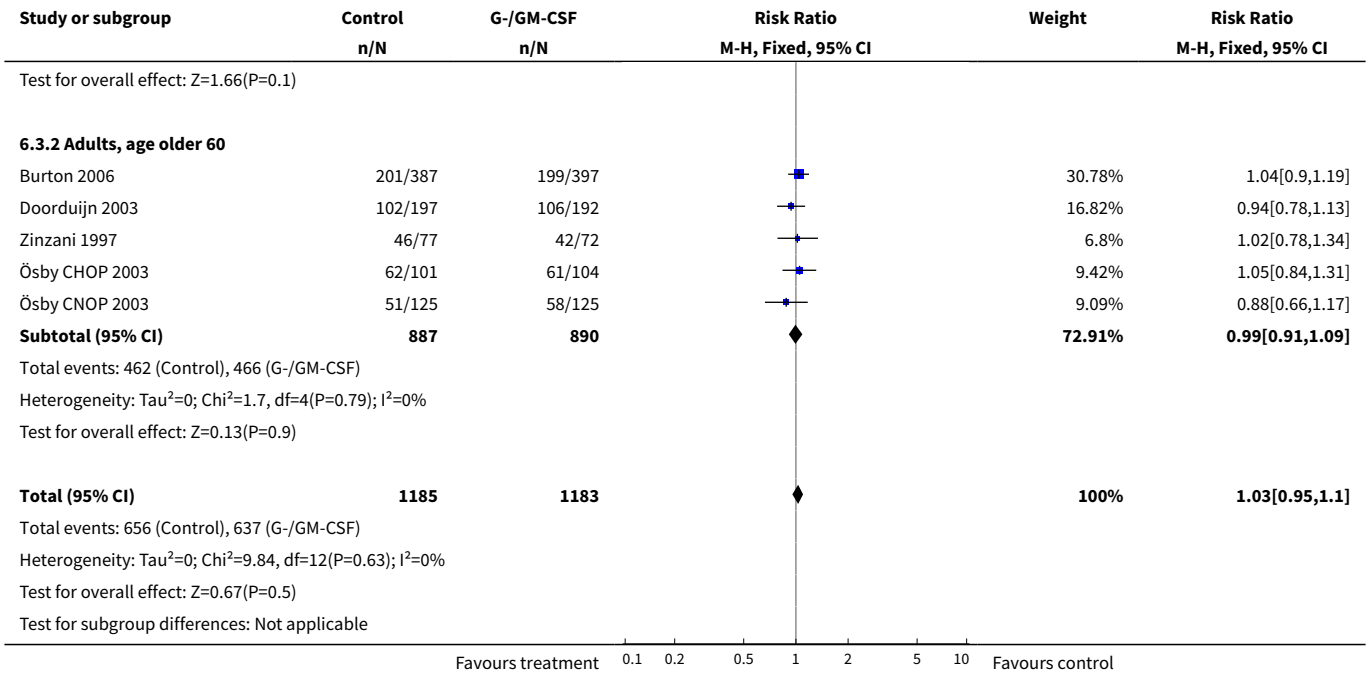
Analysis 6.2. Comparison 6 Sensitivity analysis: Complete response, Outcome 2 HD versus NHL.

Study or subgroup	Control n/N	G-/GM-CSF n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
6.2.1 Hodgkin's disease					
Aglietta 2000*	21/30	16/26		2.69%	1.14[0.78,1.67]
Dunlop MOPP 1998*	6/13	4/12		0.65%	1.38[0.51,3.74]
Dunlop MOPP/EVAP 98*	9/14	5/11		0.88%	1.41[0.66,3.01]
Subtotal (95% CI)	**57**	**49**		**4.22%**	**1.23[0.89,1.72]**
Total events: 36 (Control), 25 (G-/GM-CSF)					
Heterogeneity: Tau^2=0; Chi^2=0.35, df=2(P=0.84); I^2=0%					
Test for overall effect: Z=1.24(P=0.22)					
6.2.2 Non-Hodgkin's lymphoma					
Avilés 1994	16/20	12/22		1.79%	1.47[0.94,2.28]
Burton 2006	201/387	199/397		30.78%	1.04[0.9,1.19]
Cunningham*	3/18	1/21		0.14%	3.5[0.4,30.77]
Doorduijn 2003	102/197	106/192		16.82%	0.94[0.78,1.13]
Engelhard 1994	56/87	52/85		8.24%	1.05[0.84,1.32]
Fridrik 1997	29/35	24/36		3.71%	1.24[0.94,1.64]
Gisselbrecht 1997	54/81	57/80		8.99%	0.94[0.76,1.15]
Zinzani 1997	46/77	42/72		6.8%	1.02[0.78,1.34]
Ösby CHOP 2003	62/101	61/104		9.42%	1.05[0.84,1.31]
Ösby CNOP 2003	51/125	58/125		9.09%	0.88[0.66,1.17]
Subtotal (95% CI)	**1128**	**1134**		**95.78%**	**1.02[0.94,1.09]**
Total events: 620 (Control), 612 (G-/GM-CSF)					
Heterogeneity: Tau^2=0; Chi^2=8.53, df=9(P=0.48); I^2=0%					
Test for overall effect: Z=0.42(P=0.68)					
Total (95% CI)	**1185**	**1183**		**100%**	**1.03[0.95,1.1]**
Total events: 656 (Control), 637 (G-/GM-CSF)					
Heterogeneity: Tau^2=0; Chi^2=9.84, df=12(P=0.63); I^2=0%					
Test for overall effect: Z=0.67(P=0.5)					
Test for subgroup differences: Not applicable					

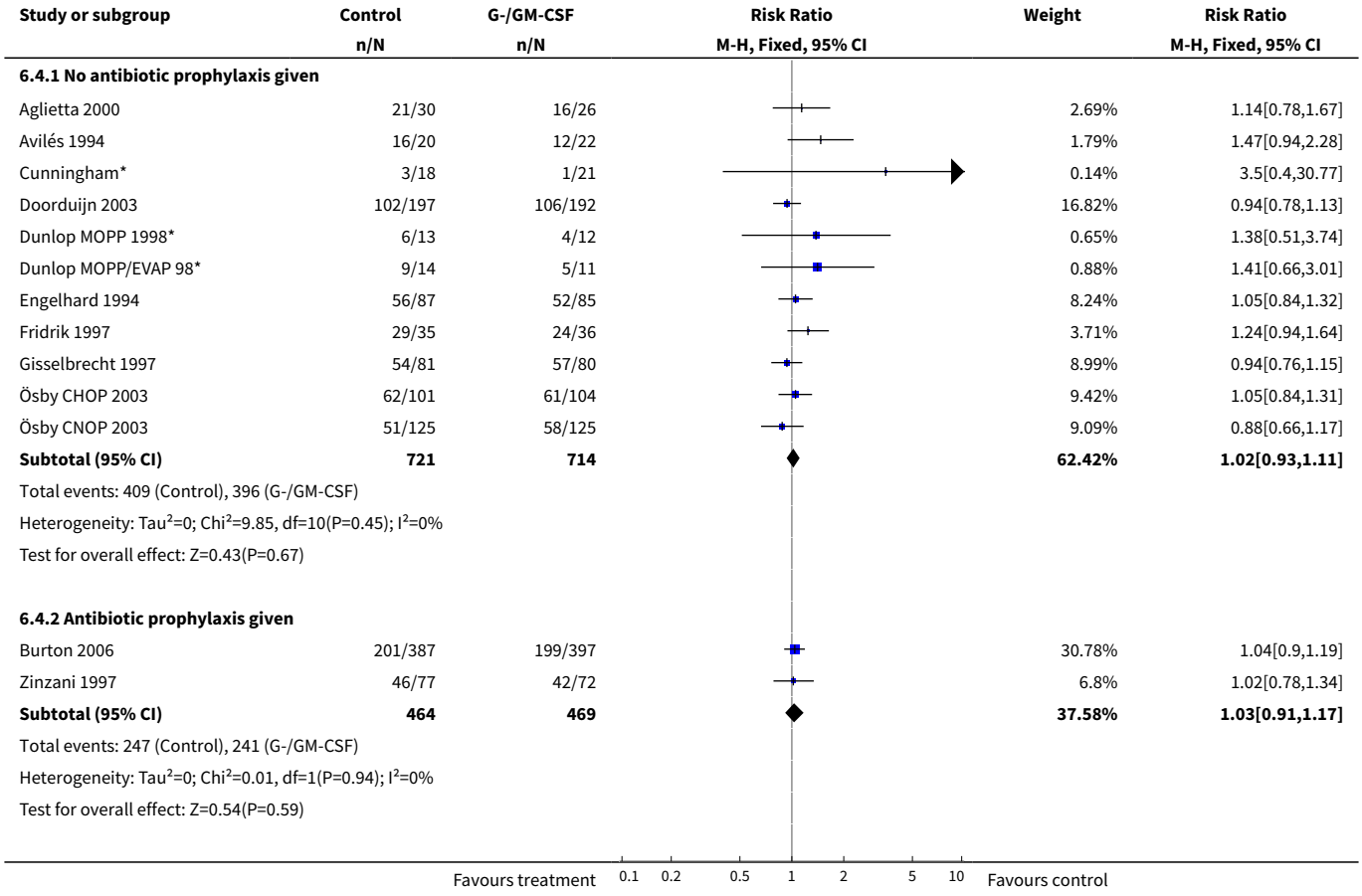


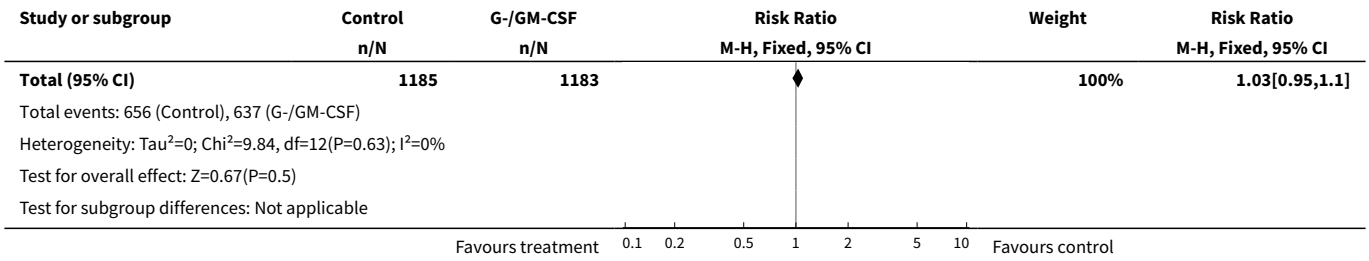
Analysis 6.3. Comparison 6 Sensitivity analysis: Complete response, Outcome 3 Age.

Study or subgroup	Control n/N	G-/GM-CSF n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
6.3.1 Adults, all ages					
Aglietta 2000	21/30	16/26		2.69%	1.14[0.78,1.67]
Avilés 1994	16/20	12/22		1.79%	1.47[0.94,2.28]
Cunningham*	3/18	1/21		0.14%	3.5[0.4,30.77]
Dunlop MOPP 1998*	6/13	4/12		0.65%	1.38[0.51,3.74]
Dunlop MOPP/EVAP 98*	9/14	5/11		0.88%	1.41[0.66,3.01]
Engelhard 1994	56/87	52/85		8.24%	1.05[0.84,1.32]
Fridrik 1997	29/35	24/36		3.71%	1.24[0.94,1.64]
Gisselbrecht 1997	54/81	57/80		8.99%	0.94[0.76,1.15]
Subtotal (95% CI)	**298**	**293**		**27.09%**	**1.11[0.98,1.25]**
Total events: 194 (Control), 171 (G-/GM-CSF)					
Heterogeneity: Tau^2=0; Chi^2=6.66, df=7(P=0.47); I^2=0%					

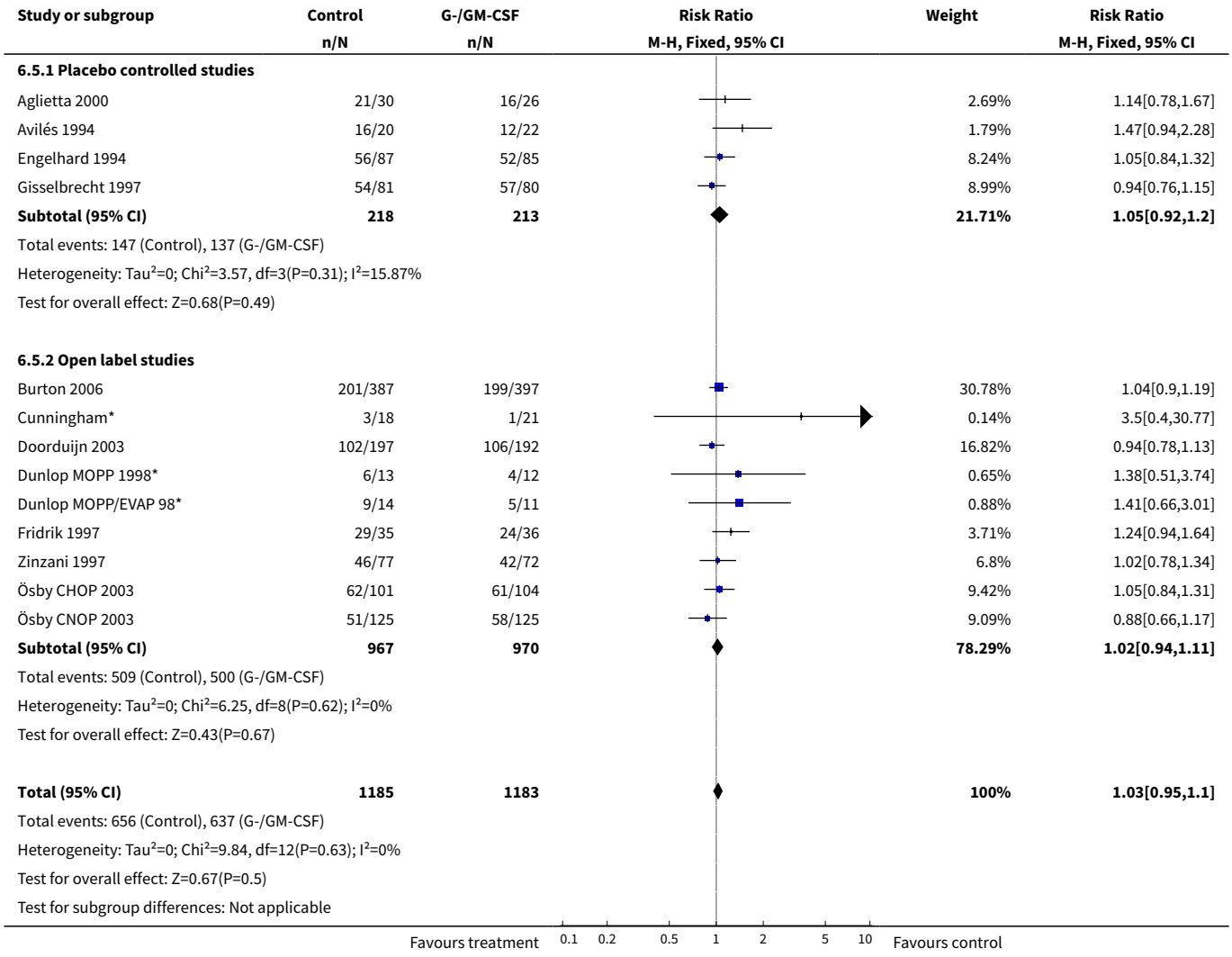


Analysis 6.4. Comparison 6 Sensitivity analysis: Complete response, Outcome 4 Use of antibiotic prophylaxis.



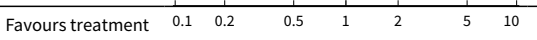


Analysis 6.5. Comparison 6 Sensitivity analysis: Complete response, Outcome 5 Blinded versus open label studies.



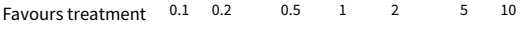
Analysis 6.6. Comparison 6 Sensitivity analysis: Complete response, Outcome 6 Published and reported data versus unpublished or unreported data.

Study or subgroup	Control n/N	G-/GM-CSF n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
6.6.1 Data not published in a peer-review journal					
Cunningham*	3/18	1/21		0.14%	3.5[0.4,30.77]
Dunlop MOPP 1998*	6/13	4/12		0.65%	1.38[0.51,3.74]
Dunlop MOPP/EVAP 98*	9/14	5/11		0.88%	1.41[0.66,3.01]
Subtotal (95% CI)	**45**	**44**		**1.67%**	**1.58[0.88,2.86]**
Total events: 18 (Control), 10 (G-/GM-CSF)					
Heterogeneity: Tau^2=0; Chi^2=0.67, df=2(P=0.72); I^2=0%					
Test for overall effect: Z=1.52(P=0.13)					
6.6.2 Peer-reviewed data					
Aglietta 2000	21/30	16/26		2.69%	1.14[0.78,1.67]
Avilés 1994	16/20	12/22		1.79%	1.47[0.94,2.28]
Burton 2006	201/387	199/397		30.78%	1.04[0.9,1.19]
Doorduijn 2003	102/197	106/192		16.82%	0.94[0.78,1.13]
Engelhard 1994	56/87	52/85		8.24%	1.05[0.84,1.32]
Fridrik 1997	29/35	24/36		3.71%	1.24[0.94,1.64]
Gisselbrecht 1997	54/81	57/80		8.99%	0.94[0.76,1.15]
Zinzani 1997	46/77	42/72		6.8%	1.02[0.78,1.34]
Ösby CHOP 2003	62/101	61/104		9.42%	1.05[0.84,1.31]
Ösby CNOP 2003	51/125	58/125		9.09%	0.88[0.66,1.17]
Subtotal (95% CI)	**1140**	**1139**		**98.33%**	**1.02[0.94,1.09]**
Total events: 638 (Control), 627 (G-/GM-CSF)					
Heterogeneity: Tau^2=0; Chi^2=7.63, df=9(P=0.57); I^2=0%					
Test for overall effect: Z=0.42(P=0.68)					
Total (95% CI)	**1185**	**1183**		**100%**	**1.03[0.95,1.1]**
Total events: 656 (Control), 637 (G-/GM-CSF)					
Heterogeneity: Tau^2=0; Chi^2=9.84, df=12(P=0.63); I^2=0%					
Test for overall effect: Z=0.67(P=0.5)					
Test for subgroup differences: Not applicable					



Analysis 6.7. Comparison 6 Sensitivity analysis: Complete response, Outcome 7 Size of studies.

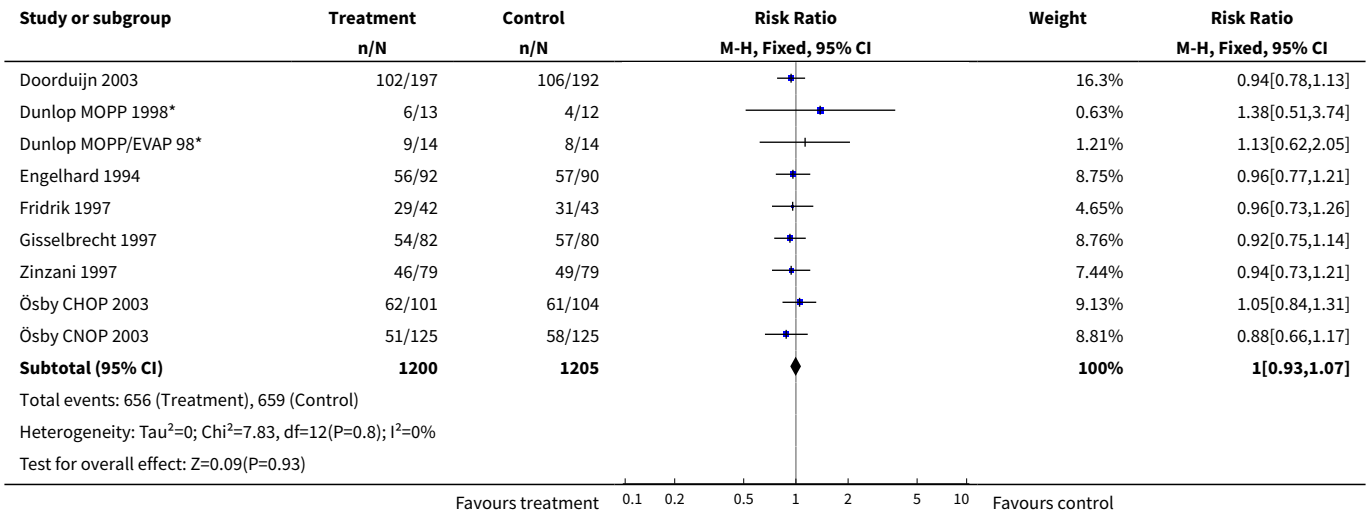
Study or subgroup	Control n/N	G-/GM-CSF n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
6.7.1 Study size n<100					
Aglietta 2000	21/30	16/26		2.69%	1.14[0.78,1.67]
Avilés 1994	16/20	12/22		1.79%	1.47[0.94,2.28]
Cunningham*	3/18	1/21		0.14%	3.5[0.4,30.77]
Dunlop MOPP 1998*	6/13	4/12		0.65%	1.38[0.51,3.74]
Dunlop MOPP/EVAP 98*	9/14	5/11		0.88%	1.41[0.66,3.01]
Fridrik 1997	29/35	24/36		3.71%	1.24[0.94,1.64]
Subtotal (95% CI)	**130**	**128**		**9.86%**	**1.31[1.08,1.6]**
Total events: 84 (Control), 62 (G-/GM-CSF)					
Heterogeneity: Tau^2=0; Chi^2=1.76, df=5(P=0.88); I^2=0%					
Test for overall effect: Z=2.7(P=0.01)					



Study or subgroup	Control n/N	G-/GM-CSF n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
6.7.2 Study size n>100					
Burton 2006	201/387	199/397		30.78%	1.04[0.9,1.19]
Doorduijn 2003	102/197	106/192		16.82%	0.94[0.78,1.13]
Engelhard 1994	56/87	52/85		8.24%	1.05[0.84,1.32]
Gisselbrecht 1997	54/81	57/80		8.99%	0.94[0.76,1.15]
Zinzani 1997	46/77	42/72		6.8%	1.02[0.78,1.34]
Ösby CHOP 2003	62/101	61/104		9.42%	1.05[0.84,1.31]
Ösby CNOP 2003	51/125	58/125		9.09%	0.88[0.66,1.17]
Subtotal (95% CI)	**1055**	**1055**		**90.14%**	**0.99[0.92,1.07]**
Total events: 572 (Control), 575 (G-/GM-CSF)					
Heterogeneity: Tau²=0; Chi²=2.26, df=6(P=0.89); I²=0%					
Test for overall effect: Z=0.16(P=0.87)					
Total (95% CI)	**1185**	**1183**		**100%**	**1.03[0.95,1.1]**
Total events: 656 (Control), 637 (G-/GM-CSF)					
Heterogeneity: Tau²=0; Chi²=9.84, df=12(P=0.63); I²=0%					
Test for overall effect: Z=0.67(P=0.5)					
Test for subgroup differences: Not applicable					

Analysis 6.8. Comparison 6 Sensitivity analysis: Complete response, Outcome 8 Worst case - best case.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
6.8.1 Best case					
Aglietta 2000	21/30	16/26		2.69%	1.14[0.78,1.67]
Avilés 1994	16/20	12/22		1.8%	1.47[0.94,2.28]
Burton 2006	201/387	199/397		30.86%	1.04[0.9,1.19]
Cunningham*	3/18	1/21		0.15%	3.5[0.4,30.77]
Doorduijn 2003	102/197	106/192		16.87%	0.94[0.78,1.13]
Dunlop MOPP 1998	6/13	4/12		0.65%	1.38[0.51,3.74]
Dunlop MOPP/EVAP 98	9/14	5/14		0.79%	1.8[0.81,4.02]
Engelhard 1994	61/92	52/90		8.26%	1.15[0.91,1.44]
Fridrik 1997	36/42	24/43		3.73%	1.54[1.15,2.06]
Gisselbrecht 1997	55/82	57/80		9.06%	0.94[0.77,1.16]
Zinzani 1997	48/79	42/79		6.6%	1.14[0.87,1.5]
Ösby CHOP 2003	62/101	61/104		9.44%	1.05[0.84,1.31]
Ösby CNOP 2003	51/125	58/125		9.11%	0.88[0.66,1.17]
Subtotal (95% CI)	**1200**	**1205**		**100%**	**1.05[0.98,1.13]**
Total events: 671 (Treatment), 637 (Control)					
Heterogeneity: Tau²=0; Chi²=16.99, df=12(P=0.15); I²=29.39%					
Test for overall effect: Z=1.45(P=0.15)					
6.8.2 Worst case					
Aglietta 2000	21/30	16/26		2.6%	1.14[0.78,1.67]
Avilés 1994	16/20	12/22		1.74%	1.47[0.94,2.28]
Burton 2006	201/387	199/397		29.83%	1.04[0.9,1.19]
Cunningham*	3/18	1/21		0.14%	3.5[0.4,30.77]



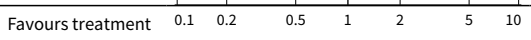
Comparison 7. Sensitivity analysis: Bone Pain

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 GM-CSF versus G-CSF	9	1204	Risk Ratio (M-H, Fixed, 95% CI)	3.57 [2.09, 6.12]
1.1 GM-CSF	2	232	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.54, 3.47]
1.2 G-CSF	7	972	Risk Ratio (M-H, Fixed, 95% CI)	5.33 [2.66, 10.68]
2 HD versus NHL	9	1204	Risk Ratio (M-H, Fixed, 95% CI)	3.57 [2.09, 6.12]
2.1 HD	1	56	Risk Ratio (M-H, Fixed, 95% CI)	1.73 [0.17, 18.04]
2.2 NHL	8	1148	Risk Ratio (M-H, Fixed, 95% CI)	3.71 [2.13, 6.45]
3 Age	9	1204	Risk Ratio (M-H, Fixed, 95% CI)	3.57 [2.09, 6.12]
3.1 Adult patients, all ages	6	600	Risk Ratio (M-H, Fixed, 95% CI)	3.17 [1.72, 5.85]
3.2 Adults patients, age older 60	3	604	Risk Ratio (M-H, Fixed, 95% CI)	5.04 [1.62, 15.65]
4 Blinding	9	1204	Risk Ratio (M-H, Fixed, 95% CI)	3.57 [2.09, 6.12]
4.1 Placebo controlled studies	4	435	Risk Ratio (M-H, Fixed, 95% CI)	2.60 [1.36, 4.98]
4.2 Open label studies	5	769	Risk Ratio (M-H, Fixed, 95% CI)	6.10 [2.27, 16.37]
5 Concealment of allocation	9	1204	Risk Ratio (M-H, Fixed, 95% CI)	3.57 [2.09, 6.12]
5.1 Allocation concealed	8	1124	Risk Ratio (M-H, Fixed, 95% CI)	3.22 [1.86, 5.59]
5.2 Unclear	1	80	Risk Ratio (M-H, Fixed, 95% CI)	14.29 [0.84, 242.02]
6 Study size	9	1204	Risk Ratio (M-H, Fixed, 95% CI)	3.57 [2.09, 6.12]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Less than 100 participants	4	263	Risk Ratio (M-H, Fixed, 95% CI)	5.60 [1.50, 20.88]
6.2 More than 100 participants	5	941	Risk Ratio (M-H, Fixed, 95% CI)	3.19 [1.77, 5.77]

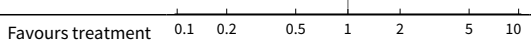
Analysis 7.1. Comparison 7 Sensitivity analysis: Bone Pain, Outcome 1 GM-CSF versus G-CSF.

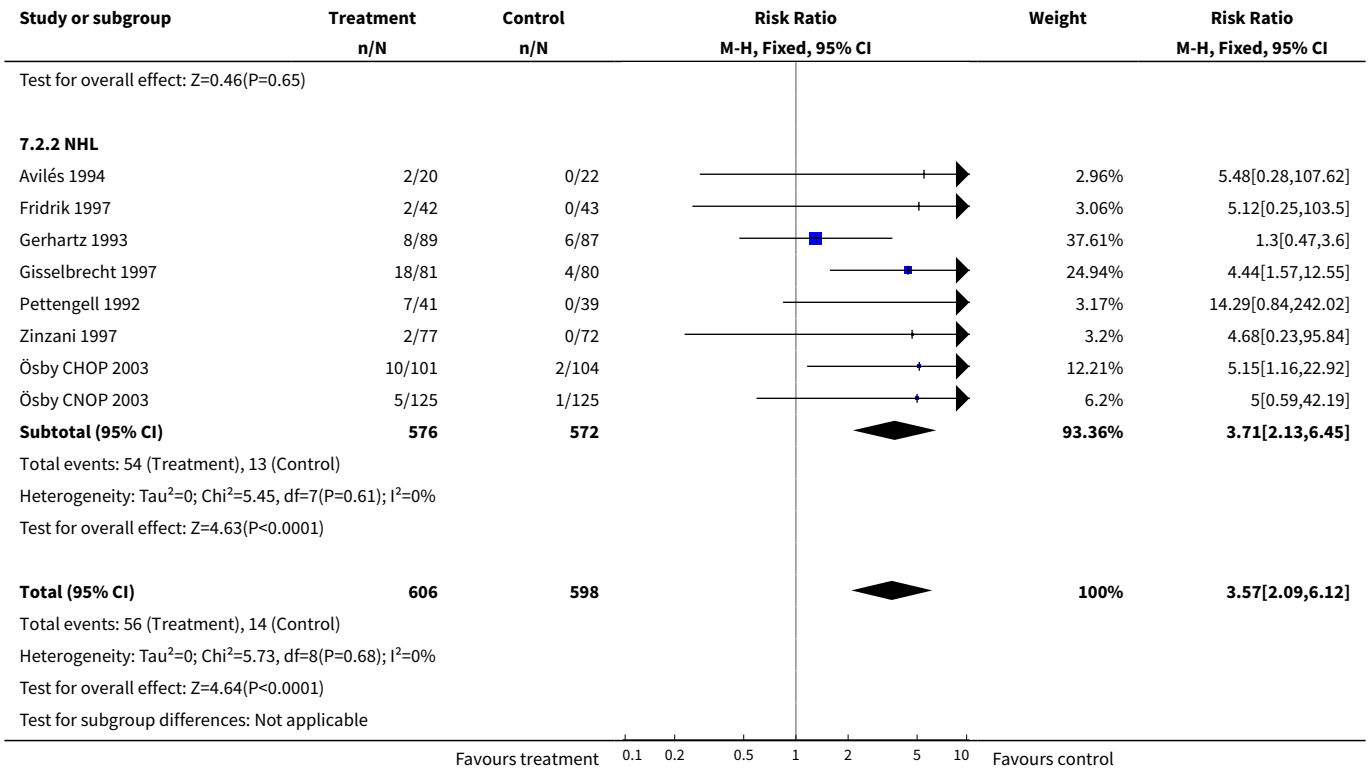
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
7.1.1 GM-CSF					
Aglietta 2000	2/30	1/26		6.64%	1.73[0.17,18.04]
Gerhartz 1993	8/89	6/87		37.61%	1.3[0.47,3.6]
Subtotal (95% CI)	**119**	**113**		**44.25%**	**1.37[0.54,3.47]**
Total events: 10 (Treatment), 7 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.05, df=1(P=0.83); I^2=0%					
Test for overall effect: Z=0.66(P=0.51)					
7.1.2 G-CSF					
Avilés 1994	2/20	0/22		2.96%	5.48[0.28,107.62]
Fridrik 1997	2/42	0/43		3.06%	5.12[0.25,103.5]
Gisselbrecht 1997	18/81	4/80		24.94%	4.44[1.57,12.55]
Pettengell 1992	7/41	0/39		3.17%	14.29[0.84,242.02]
Zinzani 1997	2/77	0/72		3.2%	4.68[0.23,95.84]
Ösby CHOP 2003	10/101	2/104		12.21%	5.15[1.16,22.92]
Ösby CNOP 2003	5/125	1/125		6.2%	5[0.59,42.19]
Subtotal (95% CI)	**487**	**485**		**55.75%**	**5.33[2.66,10.68]**
Total events: 46 (Treatment), 7 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.6, df=6(P=1); I^2=0%					
Test for overall effect: Z=4.71(P<0.0001)					
Total (95% CI)	**606**	**598**		**100%**	**3.57[2.09,6.12]**
Total events: 56 (Treatment), 14 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5.73, df=8(P=0.68); I^2=0%					
Test for overall effect: Z=4.64(P<0.0001)					
Test for subgroup differences: Not applicable					



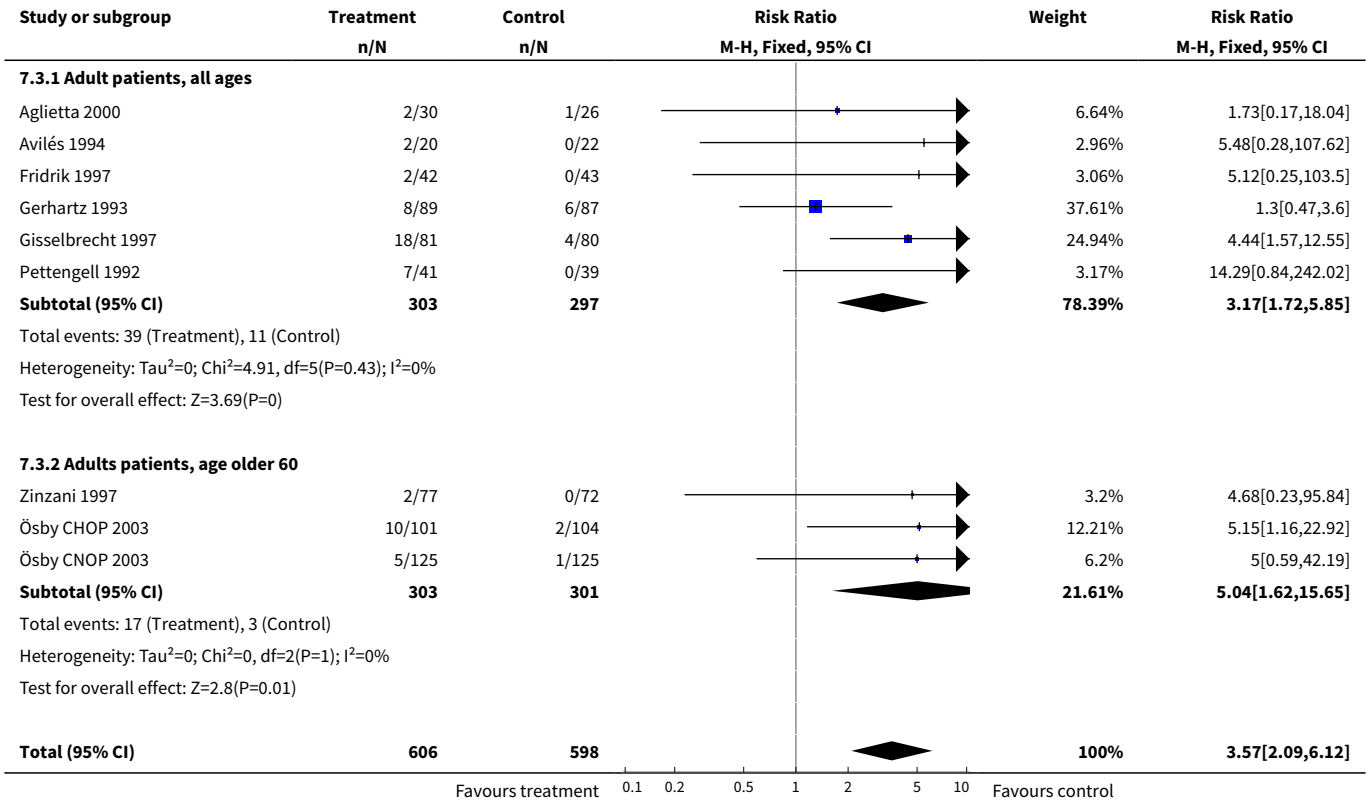
Analysis 7.2. Comparison 7 Sensitivity analysis: Bone Pain, Outcome 2 HD versus NHL.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
7.2.1 HD					
Aglietta 2000	2/30	1/26		6.64%	1.73[0.17,18.04]
Subtotal (95% CI)	**30**	**26**		**6.64%**	**1.73[0.17,18.04]**
Total events: 2 (Treatment), 1 (Control)					
Heterogeneity: Not applicable					

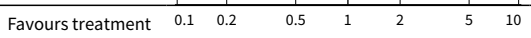




Analysis 7.3. Comparison 7 Sensitivity analysis: Bone Pain, Outcome 3 Age.

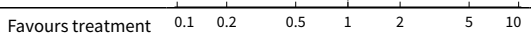


Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Total events: 56 (Treatment), 14 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5.73, df=8(P=0.68); I^2=0%					
Test for overall effect: Z=4.64(P<0.0001)					
Test for subgroup differences: Not applicable					



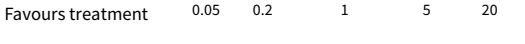
Analysis 7.4. Comparison 7 Sensitivity analysis: Bone Pain, Outcome 4 Blinding.

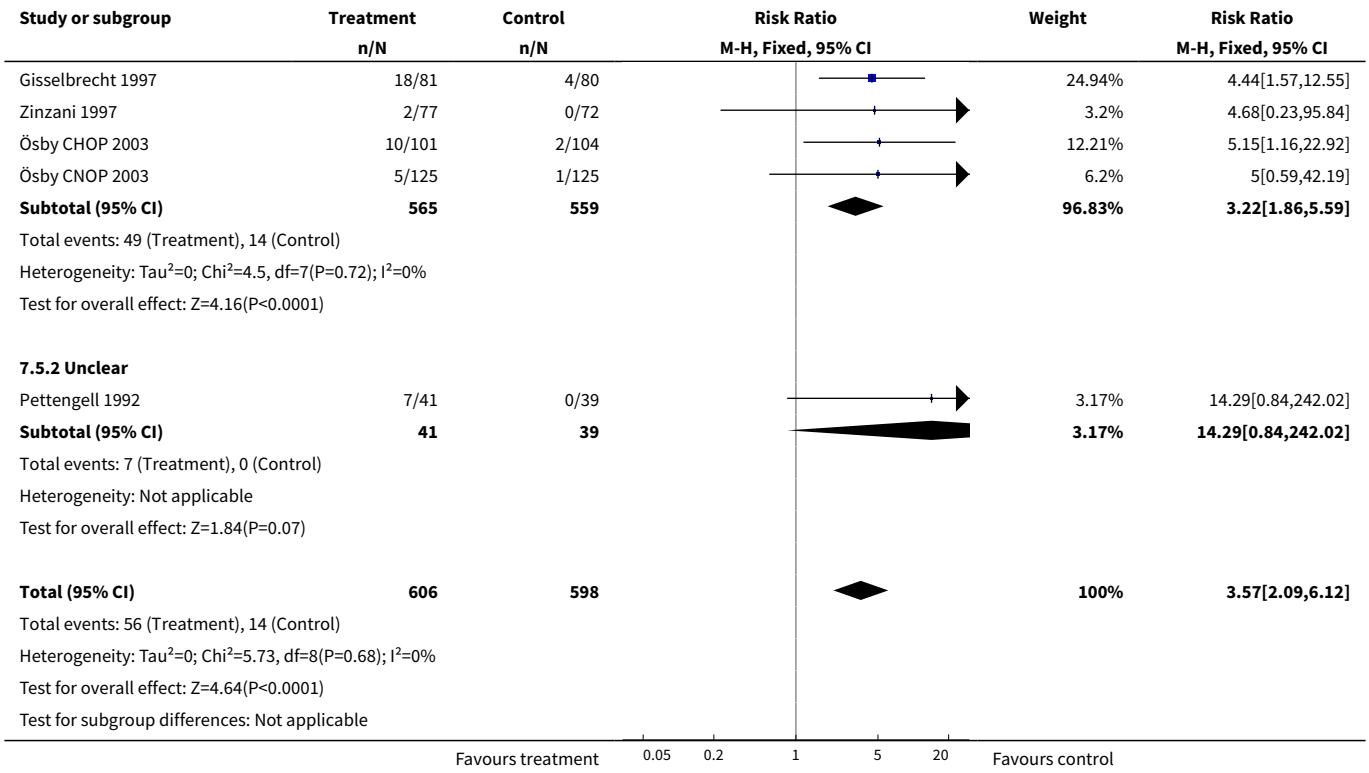
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
7.4.1 Placebo controlled studies					
Aglietta 2000	2/30	1/26		6.64%	1.73[0.17,18.04]
Avilés 1994	2/20	0/22		2.96%	5.48[0.28,107.62]
Gerhartz 1993	8/89	6/87		37.61%	1.3[0.47,3.6]
Gisselbrecht 1997	18/81	4/80		24.94%	4.44[1.57,12.55]
Subtotal (95% CI)	**220**	**215**		**72.15%**	**2.6[1.36,4.98]**
Total events: 30 (Treatment), 11 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.15, df=3(P=0.37); I^2=4.84%					
Test for overall effect: Z=2.88(P=0)					
7.4.2 Open label studies					
Fridrik 1997	2/42	0/43		3.06%	5.12[0.25,103.5]
Pettengell 1992	7/41	0/39		3.17%	14.29[0.84,242.02]
Zinzani 1997	2/77	0/72		3.2%	4.68[0.23,95.84]
Ösby CHOP 2003	10/101	2/104		12.21%	5.15[1.16,22.92]
Ösby CNOP 2003	5/125	1/125		6.2%	5[0.59,42.19]
Subtotal (95% CI)	**386**	**383**		**27.85%**	**6.1[2.27,16.37]**
Total events: 26 (Treatment), 3 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.47, df=4(P=0.98); I^2=0%					
Test for overall effect: Z=3.59(P=0)					
Total (95% CI)	**606**	**598**		**100%**	**3.57[2.09,6.12]**
Total events: 56 (Treatment), 14 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5.73, df=8(P=0.68); I^2=0%					
Test for overall effect: Z=4.64(P<0.0001)					
Test for subgroup differences: Not applicable					



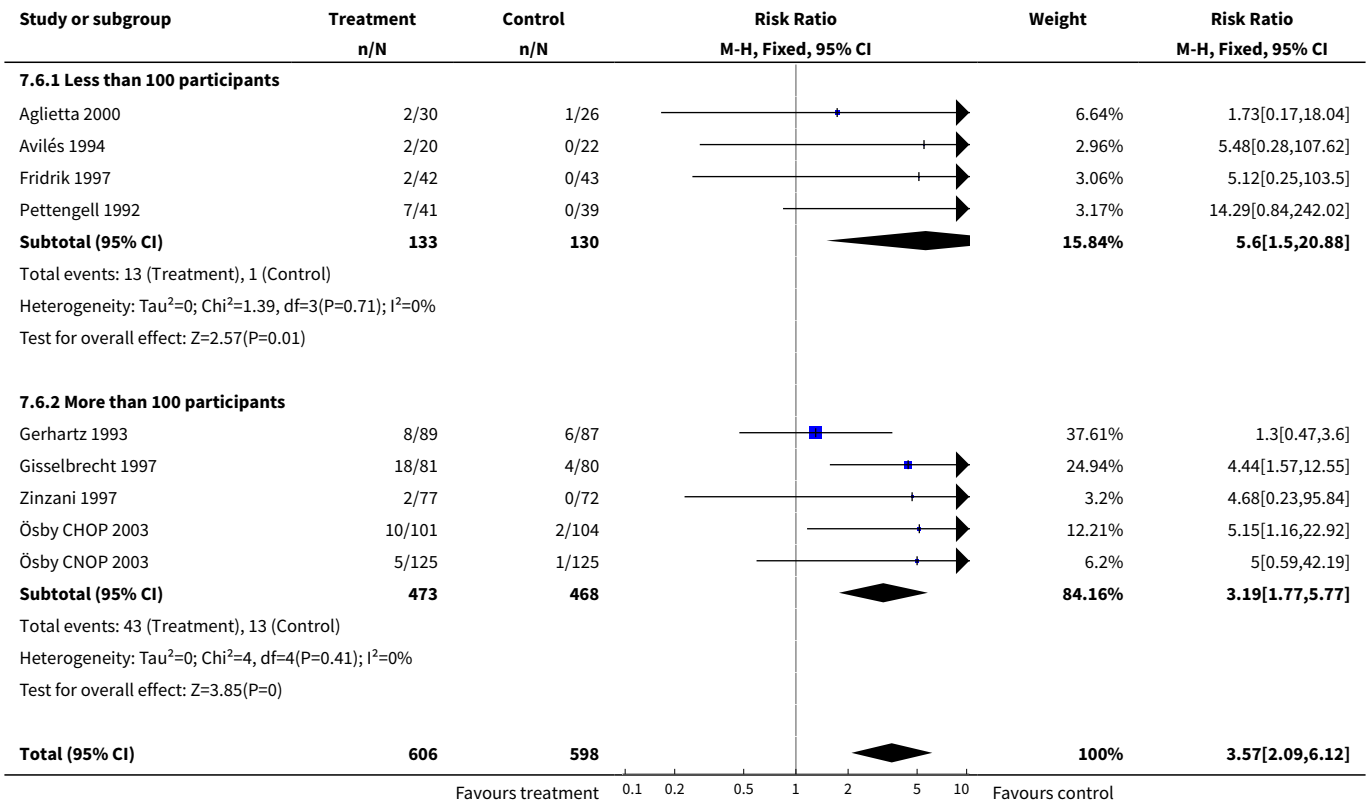
Analysis 7.5. Comparison 7 Sensitivity analysis: Bone Pain, Outcome 5 Concealment of allocation.

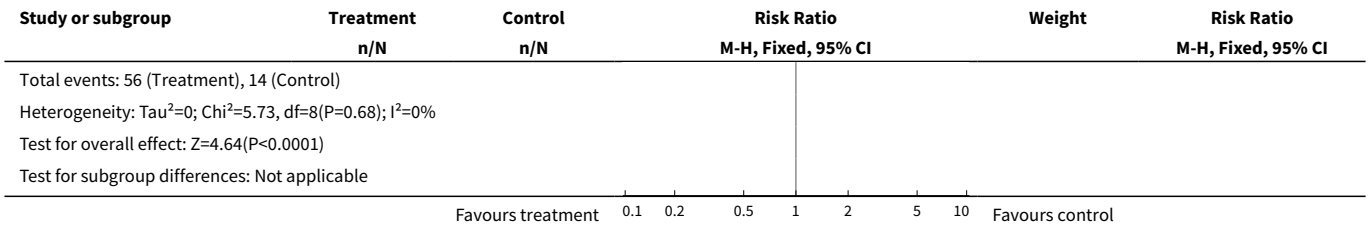
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
7.5.1 Allocation concealed					
Aglietta 2000	2/30	1/26		6.64%	1.73[0.17,18.04]
Avilés 1994	2/20	0/22		2.96%	5.48[0.28,107.62]
Fridrik 1997	2/42	0/43		3.06%	5.12[0.25,103.5]
Gerhartz 1993	8/89	6/87		37.61%	1.3[0.47,3.6]





Analysis 7.6. Comparison 7 Sensitivity analysis: Bone Pain, Outcome 6 Study size.





ADDITIONAL TABLES

Table 1. Quality Assessment

Author	Properly randomised	Concealment of allocation	Studies comparable a	Patients blinded	Physicians blinded	Outcome assessors blinded	ITT	Withdrawals stated
Aglietta 2000	Yes	Yes*	Yes	Yes	Yes	Yes	Yes	Yes
Aviles 1994	Yes	Yes*	Yes	Yes*	Yes*	Yes*	Yes	Yes
Balducci 2007	Yes	Yes	Yes	No	No	No	No	Yes
Bastion 1993	NR	NR	NR	Yes	Yes	NR	NR	NR
Burton 2006	NR	NR	Yes	No	No	NR	Yes (survival) No (neutropenia)	NR
Ösby 2003/ Björkholm 1999	Yes	Yes*	Yes	No	No	Yes*	Yes	Yes
Cunningham	Yes	Yes	Yes*	No*	No*	No*	Yes	Yes*
Dunlop MOPP 1998	Yes	Yes	Yes*	No	No	No	Yes	Yes
Dunlop MOPP/EVAP 1998	Yes	Yes	Yes*	No	No	No	No	Yes
Fridrik 1997	Yes	Yes	Yes	No	No	No	No	Yes, but
Gerhartz 1993	Yes	Yes	Yes	Yes	Yes	NR	No	Yes
Gisselbrecht 1997	Yes	Yes	Yes	Yes	Yes	No*	Yes	Yes, but
Pettengell 1992	NR	NR	Yes	No	No	No	Yes	Yes
Zinzani 1997	Yes	Yes*	Yes	No	No	No	No	No
Doorduijn 2003	Yes	Yes*	Yes	No	No	No	Yes	Yes

Table 2. Duration of neutropenia

Author	Outcome	G-/GM-CSF	Control	P value	Comments
Aglietta 2000	mean duraction of neutropenia in days, ANC < 500	9.77, SD = 14.87, N = 30	11.85, SD = 12.79, N = 26	not significant	
Avilés 1994	mean duration of neutropenia in days (ANC < 1000)	2.1, number of neutropenic episodes:7	15.4, number of neutropenic episodes: 41	?	P value not stated
	median duration of neutropenia in days (ANC < 1000)	2.1, SD = 0.5, number of neutropenic episodes:7	8.3, SD = 1.6, number of neutropenic episodes: 41	?	P value not stated
Gisselbrecht 1997	1. cycle, median duration of neutropenia in days (ANC <500)	1 (range 0-8), N = 80	4 (range 0-3), N = 80	P < 0.001	similar dataset available for ANC < 1000
	2. cycle, median duration of neutropenia in days (ANC <500)	1 (range 0-6), N = 79	4 (range 0-15), N = 73	P < 0.001	
	3. cycle, median duration of neutropenia in days (ANC <500)	0 (range 0-5), N = 76	3 (range 0-14), N = 67	P < 0.001	
	4. cycle, median duration of neutropenia in days (ANC <500)	1 (range 0-9), N = 74	2 (range 0-10), N = 63	P < 0.001	
Dunlop MOPP 1998	median duration of leucopenia (days/cycle with WBC <1x109/L	0.0 (range 0.0-4.3)	2.9 (range 0.0-8.6)	P = 0.007	
Dunlop MOPP/EVAP 98	median duration of leucopenia (days/cycle with WBC <1x109/L	1.5 (range 0.0-6.2)	0.8 (range 0.0-9.1)	P = 0.26	

Table 3. Duration of febrile neutropenia

Author	Outcome	G-/GM-CSF	Control	P value	Comments
Avilés 1994	median duration of febrile episodes in days, ANC < 500, T: 38.5°C	2.1, SD = 0.5, N =7	8.3, SD = 1.6, N = 41 (number of febrile episodes)	?	P value not stated
Dunlop MOPP 1998	median duration in days, ANC < 1000, T: > 38.2°C	1 patient had FN of unknown duration	4 pts had FN, duration 1,2 , 3, 7 days		
Dunlop MOPP/EVAP 98	median duration in days, ANC < 1000, T: > 38.2°C	6 patients had FN, duration: 1, 1, 2, 2, 5, 9 days	5 pts had FN, duration 1, 1, 2, 3.5, 20 days		

Table 3. Duration of febrile neutropenia *(Continued)*

Fridrik 1997	median duration in days, ANC < 1000, T: > 37.5°C twice or > 38°C once	0, range 0-14, N = 36	1, range 0-14, N = 36	
Doorduijn 2003	median duration in days	2, range 1-14, N = 197	3, range 1-32, N = 192	0.04

Table 4. Stay in hospital

Author	Outcome	G-CSF/GM-CSF	Control	P value	Comments
Avilés 1994	number of hospitalised days	67 days (N = 20)	389 days (N = 22)		range or standard deviation not stated, P values not specified
Dunlop MOPP 1998	median number of days of inpatient hospitalisation per cycle of chemotherapy	0.2 days (range 0.0-14.6, N = 13)	2.21 days (range 0.0-14.6, N = 12)	not significant	P values not specified
Dunlop MOPP/ EVAP 98	median number of days of inpatient hospitalisation per cycle of chemotherapy	2.7 days (range 0.2-8.3, N = 12)	1.2 days (range 0.08-8.4, N = 10)	not significant	P values not specified
Gerhartz 1993	mean number of days in hospital for infection	3.5 days (N = 59)	8.0 days (N = 66)	P = 0.01	range or standard deviation has not been stated
Pettengell 1992	number of patients hospitalised for more than 3 days for infection	20/41	20/39	not significant	P values not specified
Souêtre 1994	mean number of days, chemotherapy-related services	11.9 days (SD: 7.1, N = 82)	11.4 days (SD:6.8, N = 80)	0.61	
	mean number of days, chemotherapy-unrelated services	14.4 days (SD:10.5, N = 82)	18.5 days (SD:12.6, N = 80)	0.04	
Doorduijn 2003	median overall number of days in hospital	5 days (range: 0-157, N =197)	6 days (range 0-111, N =192)	0.40	

Table 5. Duration of antibiotic use

Author	Outcome	G-/GM-CSF	Control	P value	Comments
Aglietta 2000	mean duration of antibiotic treatment	14.9, SD = 61.50, N = 30	18.4, SD = 47.70, N = 26	P = 0.8	antibiotic use is not differentiated for iv and po medication
Souêtre 1994	mean duration of iv antibiotic treatment	5.30, SD = 7.80, N = 82	8.90, SD = 8.80, N = 80	P = 0.006	same patient population as Gisselbrecht 1997

Table 5. Duration of antibiotic use *(Continued)*

Doorduijn 2003	median duration of antibiotic treatment	0 days (range 0-126, N = 197)	6 days (range 0-180, N = 192)	P = 0.006

Table 6. Relative Dose Intensity

Author	Dose Intensity	Substance	G-/GM-CSF	Control	P value	comments
Avilés 1994	defined as by Hryniuk	Cyclophosphamide	73%, N =20	61%, N =22	-	P values were not specified. Overall more chemotherapeutic substances were used, but RDI not calculated by the study author. Not stated whether mean or median values.
		Epirubicin	82%	51%	-	
		Etoposide	83%	67%	-	
		Cytosine arabinoside	79%	53%	-	
		Mitoxantrone	87%	49%	-	
		Procarbazine	89%	60%	-	
Ösby 2003	mean cumulative received dose intensity in cycle 8	Doxorubicin, Mitoxantrone, Cyclophosphamide	CHOP: 92.6, SD = 9.4, CNOP: 92.3, SD = 8.68	CHOP: 88.8, SD = 10.09, CNOP: 89.8, SD = 10.17	not significant	
Dunlop MOPP 1998	median received dose intensity	MOPP	84%, range 59-103%, N =1 3	82%, range 57-99%, N = 12	P = 0.57	
Dunlop MOPP/ EVAP 98	median received dose intensity	MOPP/EVAP	96%, range 67-105%, N = 12	97%, range 71-104%, N = 10	P = 0.53	
Fridrik 1997	defined as by Hryniuk	CEOP-IMVP-Dexa	82.3%, N = 38	76.2%, N = 36	P = 0.041	not stated whether mean or median
Gerhartz 1993	defined as by Hryniuk; median received dose intensity	COP-BLAM	median =85%, mean = 85%	median = 84%, mean = 81%	-	efficiency analysis: based only on patients, that received more than 70% of the study drug, 137 of 172 pts evaluated
Gisselbrecht 1997	defined as by Hryniuk, mean received dose intensity	adriamycin and cyclophosphamide	93.3%, SD = 13.5, N = 73	80.1%, SD = 13, N = 63	P = 0.0001	evaluable for this analysis, more different substances were administered, but not calculated for RDI, only 136 of 162 pts evaluated

Table 6. Relative Dose Intensity *(Continued)*

Pettengell 1992	defined as by Hryniuk, median received dose intensity	Adriamycin	96%, N = 39	85%, N = 41	P = 0.0004	
		Cyclophos-phamide	96%	83%	P = 0.0001	
		Etoposide	94%	82%	P = 0.02	
Zinzani 1997	defined as by Hryniuk	VNCOP-B	95%, N = 77	85%, N = 72	not signif-icant	not stated whether mean or median
Doorduijn 2003	median received dose intensity	Cyclophos-phamide	96.3%	93.9%	P = 0.01	
		Doxorubicin	95.4%	93.3%	P = 0.04	
		overall CHOP	95.1%	93.4%	not signif-icant	

Table 7. Thrombocytopenia

Author	outcome	G-CSF/GM-CSF	control	P value	comments
Dunlop MOPP 1998	median platelets nadir [/µl]	41, range 6-193, N =13	30, range 7-253, N = 12	not signif-icant	P values not specified
Dunlop MOPP/EVAP 98	median platelets nadir [/µl]	14, range1-76, N = 12	65, range 6-168, N = 10	not signif-icant	P values not specified
Fridrik 1997	mean platelet nadir [/µl]	95, N = 38	152, N = 36	P = 0.000004	range or standard devia-tion not specified
Gerhartz 1993	incidence of thrombocytopenia < 25/ µl	8/89	4/87	not signif-icant	P values not specified
Aglietta 2000	incidence of thrombocytopenia < 50 / µl	0/30	2/26	not signif-icant	P values not specified
Pettengell 1992	incidence of thrombocytopenia and platelets transfusion requirements	similar in both groups	similar in both groups		no numerical data speci-fied
Zinzani 1997	incidence of thrombocytopenia	similar in both groups	similar in both groups		no numerical data speci-fied

Table 8. Anaemia

Author	Outcome	G-CSF/GM-CSF	Control	P value	comments

Table 8. Anaemia *(Continued)*

Dunlop MOPP 1998	median haemoglobin nadir [g/dl]	8.1, range 6.3-10.1, N = 13	7.4, range 4.9-11.3, N = 12	not significant	P values not specified
Dunlop MOPP/EVAP 98	median haemoglobin nadir [g/dl]	7.2, range 4.6-8.5, N = 12	8.6, range 7.3-9.7, N = 10	not significant	P values not specified
Fridrik 1997	mean haemoglobin nadir [g/dl]	8.395, N = 38	9.278, N = 36	P = 0.00558	range or standard deviation not specified
Pettengell 1992	incidence of anaemia and transfusion requirements	similar in both groups	similar in both groups		no numerical data specified
Zinzani 1997	incidence of anaemia	similar in both groups	similar in both groups		no numerical data specified

APPENDICES

Appendix 1. MEDLINE search strategy

#1 the highly sensitive strategy for identifying reports of randomised controlled trials (Dickersin 1994)
#2 G?CSF*
#3 GM?CSF*
#4 CSF*
#5 RHUG?CSF*
#6 RHUGM?CSF*
#7 RHG?CSF*
#8 RHGM?CSF*
#9 R?METHUG?CSF*
#10 (H?EMATO* near GROWTH* near FACTOR*)
#11 ((COLON* near STIMULAT*) near FACTOR*)
#12 (GRANULO?YT* near FA?TOR*)
#13 (MA?ROPHAG* near FA?TOR*)
#14 FILGRASTIM*
#15 LENOGRASTIM*
#16 REGRARMOSTIM*
#17 ECOGRARMOSTIM*
#18 MOLGRARMOSTIM*
#19 SARGRARMOSTIM*
#20 NEUPOGEN*
#21 LEUKINE
#22 LEUCOMAX
#23 GRANOCYTE
#24 COLONY-STIMULATING-FACTORS*:ME
#25 (#2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24)
#26 LYMPHOMA*:ME
#27 HEMATOLOGIC-NEOPLASMS*:ME
#28 LYMPHOM*
#29 HODGKIN*
#30 NON-HODGKIN*
#31 NONHODGKIN*
#32 IMMUNO?YTOM*
#33 ((HAIR* next CELL*) near Leu*)
#34 BURKIT*

#35 SEZARY*
#36 (MYCOS* next FUNGO*)
#37 (HEMATO* near MALIGN*)
#38 (HAEMATO* near MALIGN*)
#39 (HEMATO* near NEOPLAS*)
#40 (HAEMATO* near NEOPLAS*)
#41 (#26 or #27 or #28 or #29 or #30 or #31or #32 or #33 or #34 or #35 or #36 or #37or #38 or #39 or #40)
#42 (#1 and #25 and #41)

WHAT'S NEW

Date	Event	Description
8 June 2008	New search has been performed	Review updated
7 June 2008	New citation required but conclusions have not changed	A new search was done in April 2008, with one additional study identified. A total of 13 randomized controlled trials were included in this review update.

HISTORY

Protocol first published: Issue 3, 2001
Review first published: Issue 2, 2002

Date	Event	Description
22 April 2004	New citation required and conclusions have changed	Substantive amendment. We identified one full text publication (Ösby 2003) to a study which was previously included on the basis of an abstract publication (Björkholm 1999). Additionally we identified one study which has been recently published (Doorduijn 2003). Of these publications we included only reported data. Updating the review we include now 12 trials with 1.823 patients. Compared to the old version with 11 studies and 1.434 patients none of the results changed significantly. We now include results on Quality of Life.

CONTRIBUTIONS OF AUTHORS

JULIA BOHLIUS: Protocol development, searching for trials, eligibility and quality assessment, data extraction and analysis, drafting of final review, updating review

ANDREAS ENGERT: Clinical and scientific advice, assessment of eligibility and quality, data analysis, content input

CHRISTINE HERBST: Update: abstract screening, eligibility and quality assessment, data extraction and analysis, drafting of the updated review

MARCEL REISER: Searching for trials, assessment of eligibility and quality, data extraction and analysis, content input

GUIDO SCHWARZER: Statisticaladvice and data analysis

DECLARATIONS OF INTEREST

Chugai Pharma (Chugai Pharma Marketing Ltd., Subsidiary Germany, Frankfurt/Main) provided the translation of a Japanese publication (Togawa 2000) for the Cochrane Haematological Malignancies Group. Andreas Engert received research funding and honoraria from Amgen Ltd. for other projects.

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  Department of Health, England

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Agents [*adverse effects]; Fever [chemically induced] [*prevention & control]; Granulocyte Colony-Stimulating Factor [*therapeutic use]; Granulocyte-Macrophage Colony-Stimulating Factor [*therapeutic use]; Lymphoma [*drug therapy]; Neutropenia [chemically induced] [*prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Humans