Primary prophylactic colony-stimulating factors for the prevention of chemotherapy-induced febrile neutropenia in breast cancer patients (Review)

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[Intervention Review]

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ABSTRACT

Background

High-dose or dose-intensive cytotoxic chemotherapy often causes myelosuppression and severe neutropenia among cancer patients. Severe neutropenia accompanied by fever, named febrile neutropenia (FN), is the most serious manifestation of neutropenia usually requiring hospitalization and intravenous antibiotics. FN and neutropenia can lead to chemotherapy treatment delays or dose reductions, which potentially compromises the effectiveness of cancer treatment and prospects for a cure. Granulocyte-macrophage (GM) and granulocyte colony-stimulating factors (G-CSFs) are administered during chemotherapy in order to prevent or reduce the incidence or the duration of FN and neutropenia.

Objectives

To assess the effect of prophylactic colony-stimulating factors (CSFs) in reducing the incidence and duration of FN, and all-cause and infection-related mortality during chemotherapy in patients with breast cancer.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, HEALTHSTAR, International Health Technology Assessment, SOMED, AMED and BIOSIS up to 8 August 2011. We also searched three Chinese databases (VIP, CNKI, CBM), the metaRegister of Controlled Trials, ClinicalTrials.gov, the World Health Organization's International Clinical Trials Registry Platform (WHO ICTRP) and OpenGrey.eu up to August 2011.

Selection criteria

Randomized controlled trials (RCTs) comparing CSFs (any dose) with placebo or no treatment in patients with breast cancer at any stage, at risk of developing FN while undergoing any type of chemotherapy.

Data collection and analysis

We used pooled risk ratios (RR) with 95% confidence intervals (CIs) for binary outcomes. At least two review authors independently extracted data and assessed the risk of bias of the included studies. Trial authors were contacted for further details when information was unclear.

Main results

We included eight RCTs involving 2156 participants with different stages of breast cancer and chemotherapy regimens. The trials were carried out between 1995 and 2008 and judged as being at least at moderate risk of bias. The strength of the evidence was weak for the majority of outcomes, which was mostly because of the small numbers of evaluable patients, varying definitions, as well as unclear measurements of the trials' outcomes and uncertain influences of supportive treatments on them. In most trials, the chemotherapy regimens had a risk of FN that was below the threshold at which current guidelines recommend routine primary prophylaxis with CSFs. Using CSFs significantly reduced the proportion of patients with FN (RR 0.27; 95% CI 0.11 to 0.70; number needed to treat for an additional beneficial outcome (NNTB) 12) but there was substantial heterogeneity which can be explained by possible differential effects of G-CSFs and GM-CSFs and different definitions of FN. A significant reduction in early mortality was observed in CSF-treated patients compared to placebo or no treatment (RR 0.32; 95% CI 0.13 to 0.77; NNTB 79). This finding was based on 23 fatal events in 2143 patients; wherein 19 of these 23 events occurred in one study and 17 events were attributed to progression of the disease by the study authors. For infection-related mortality, there were no significant differences between CSF and control groups (RR 0.14; 95% CI 0.02 to 1.29). In CSF-treated patients, the risk for hospitalization was significantly reduced (RR 0.14; 95% CI 0.06 to 0.30; NNTB 13), as well as the use of intravenous antibiotics (RR 0.35; 95% CI 0.22 to 0.55; NNTB 18). The risks of severe neutropenia, infection or not maintaining the scheduled dose of chemotherapy did not differ between CSF-treated and control groups. CSFs frequently led to bone pain (RR 5.88; 95% CI 2.54 to 13.60; number needed to treat for an additional harmful outcome (NNTH) 3) and injection-site reactions (RR 3.59; 95% CI 2.33 to 5.53; NNTH 3).

Authors' conclusions

In patients with breast cancer receiving chemotherapy, CSFs have shown evidence of benefi t in the prevention of FN. There is evidence, though less reliable, of a decrease of all-cause mortality during chemotherapy and a reduced need for hospital care. No reliable evidence was found for a reduction of infection-related mortality, a higher dose intensity of chemotherapy with CSFs or diminished rates of severe neutropenia and infections. The majority of adverse events reported from CSF use were bone pain and injection-site reactions but no conclusions could be drawn regarding late-term side effects.

PLAIN LANGUAGE SUMMARY

Prophylactic colony-stimulating factors to prevent infectious complications in patients with breast cancer undergoing chemotherapy

Patients with breast cancer receiving chemotherapy have an increased risk of infection mediated through a low number of protective white blood cells (neutropenia). Neutropenia is a common toxicity of many chemotherapy agents and is caused by the suppression of the bone marrow. The first sign of infection is usually a fever, which indicates a potentially life-threatening condition if it occurs during severe neutropenia (febrile neutropenia (FN)). FN requires hospital care including the administration of intravenous antibiotics and possible delays in the continuation of chemotherapy. Colony-stimulating factors (CSFs) are drugs administered during chemotherapy in order to prevent or reduce the incidence or duration of FN and neutropenia. This review included eight trials in which 2156 patients with breast cancer had randomly received CSFs or placebo or no treatment during chemotherapy. These trials were carried out between 1995 and 2008. Prophylactic treatment with CSFs significantly reduced the risk of developing FN by 73%. The estimated number of patients needed to be treated with CSFs in order to prevent one event of FN was 12. Although a significant decrease in mortality of all causes during chemotherapy and CSF therapy was noted, there was no reduction in infection-related mortality. There was no significant effect observed that planned chemotherapy schedules could be better maintained if CSFs were administered or that the number of patients with neutropenia decreased with CSFs. Notably, CSFs significantly reduced the need for hospital care yet frequently caused short-term adverse effects like bone pain and injection-site reactions. There were several limitations in this analysis: only a few trials could be included, the number of patients was low in many of these trials, and disease stages and chemotherapy treatments varied considerably. Moreover, the trial authors defined their outcomes differently, making comparisons across studies difficult. Information on the primary and secondary outcomes could not be obtained from all trials and the overall reporting quality was low. Many studies were dated and hence the administration of CSFs did not comply with current recommendations. Overall, CSFs have shown moderate evidence of bene

fi t in the prevention of FN in patients with breast cancer receiving chemotherapy. The evidence that the administration of CSFs could reduce early mortality of all causes was weak and substantiates the need of further studies. There was no reduction in risk of infection-related mortality with CSF treatment.

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

Prevention of chemotherapy-induced FN in breast cancer patients - primary outcomes

Patient or population: breast cancer patients undergoing chemotherapy
Settings: randomized controlled trials
Intervention: primary prophylactic G-CSF/GM-CSF

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Primary prophylactic G-CSF/GM-CSF				
Febrile neutropenia Rates of patients	**153 per 1000**	**57 per 1000** (44 to 72)	**RR 0.27** (0.11 to 0.70)	2073 (6 studies)	⊕⊕⊕◯ **moderate**[1,2]	
Early mortality Rates of patients	**18 per 1000**	**6 per 1000** (2 to 14)	**RR 0.32** (0.13 to 0.77)	2143 (8 studies)	⊕⊕◯◯ **low**[2,3]	
Infection-related mortality Rates of patients	**3 per 1000**	**0 per 1000** (0 to 4)	**RR 0.14** (0.02 to 1.29)	2143 (8 studies)	⊕⊕◯◯ **low**[2,4]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; G-CSF: granulocyte colony-stimulating factors; GM-CSF: granulocyte-macrophage colony-stimulating factors; RR: risk ratio

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

[1] Varying definitions of outcome; unclear schedules of measurement of outcome; possible influence on outcome by different supportive treatments.

[2] Studies on average at moderate risk of bias.
[3] Effect mainly based on one study; post-hoc analyses; very low number of events; attribution of reasons for death unclear.
[4] Low reporting quality of outcome; very low number of events; post-hoc analyses; possible influence on outcome by different supportive treatments between groups.

BACKGROUND

Description of the condition

Chemotherapy still plays a major role in the treatment of patients with breast cancer. It is widely used as an adjuvant treatment in patients following primary removal of tumors to attain cure and to prevent recurrence, and as a palliative treatment in patients with metastatic disease. Palliative chemotherapy aims to induce tumor remission, to prolong survival, to control symptoms, and to maintain or improve quality of life. As with any other treatment, the potential benefits of either adjuvant or palliative chemotherapy for breast cancer must be balanced against the potential risks of treatment-related morbidity and mortality. Chemotherapy causes a wide range of adverse effects and can result in symptoms that are debilitating and that seriously impact on patients' quality of life. Nausea and vomiting, loss of hair and changes in blood cell counts constitute the most frequent, acute adverse effects. The changes in blood cell counts comprise a decrease in the number of red cells (anemia), platelets (thrombocytopenia) and white blood cells (leukopenia). While leukopenia means a decrease of all types of white blood cells, the term neutropenia describes a diminished number of neutrophil granulocytes. Neutrophils act as the first line of cellular defense against infectious agents. An episode of fever during the period of neutropenia is called febrile neutropenia (FN). FN is defined as a rise in axillary temperature to > 38.5 °C for a duration of more than one hour while having an absolute neutrophil count (ANC) of less than 0.5×10^9/L (Crawford 2010). The risk of FN is directly related to the severity and duration of neutropenia (Bodey 1966). Although FN does not necessarily imply a documentable infection, it is most likely an indicator of some infectious condition. Once it occurs there is little chance to clarify the reasons (bacteria, virus, fungi, tumor-related) within a short period of time. Therefore FN is always managed like a severe infection. Infectious complications during neutropenia are potentially life threatening and mortality rates associated with FN range from 2% to 21% (Smith 2006). Episodes of FN not only increase the costs of treatment through the required hospitalization (Crawford 2004) but could also lead to delays of chemotherapy or necessitate dose-reduction of chemotherapy. However, this creates a difficult clinical situation since the timing and dosage of cytotoxic substances are crucial elements that determine the success of a chemotherapeutic treatment (Samson 1984). Hence, reducing dose intensity or dose density of chemotherapy is clinically undesirable as it might jeopardize its effectiveness.

Description of the intervention

During the 1960s, the concept of the formation of mature blood cells from hematopoietic stem cells was established on an experimental basis using mainly murine assays. Immature cells from bone marrow, when given to culture plates, give rise to different colonies or colony-forming units (CFU), as bacteria do when plated on agar (Bradley 1966; Pike 1970). For the myeloid lineage, these aggregates were termed colony-forming unit granulocyte macrophage (CFU-GM) and colony-forming unit granulocyte (CFU-G). Two distinct cytokines called colony-stimulating factors (CSFs) were found to induce each type of the observed colonies: GM-CSF and G-CSF. Both CSFs became available for clinical use during the late 1980s and different types of GM-CSF and G-CSF are available on the market. Filgrastim and lenograstim are the most commonly used G-CSFs and sargramostim and molgramostim are the most commonly used GM-CSFs. Since 2002, a long-acting form of filgrastim linked to polyethylene glycol, pegfilgrastim, and several officially approved subsequent versions of filgrastim, so-called biosimilars, have been available (Jelkmann 2010; Petros 2003). G-CSFs and, to a much lesser extent, GM-CSFs are being used during chemotherapy in patients with breast cancer for two main purposes: (1) as concomitant treatment to antibiotics in febrile neutropenic patients or (2) as prophylactic treatment either starting with the first cycle of chemotherapy if neutropenia is likely to occur, or in cases where severe neutropenia is already documented (primary prophylaxis), or in patients who have already experienced infectious complications during neutropenia in earlier cycles of chemotherapy (secondary prophylaxis).

How the intervention might work

GM-CSFs expand the compartment of granulocyte and monocyte precursor cells in the bone marrow, thereby increasing the number of mature granulocytes and monocytes in the blood stream. The action of G-CSFs is not restricted but concentrated to the granulocyte lineage, leading not only to a dramatic increase of neutrophils in the peripheral blood (Lyman 2010), but also a reduction in the maturation time from stem cell to the neutrophil granulocyte (Lyman 2010). In addition to their growth promoting actions, CSFs exert effects on phagocytosis, motility, bactericidal activity, and surface molecule expression of neutrophils and monocytes (Carulli 1997; Fazzi 2007). Hence, the efficacy of CSFs is believed to not only function via a shortening of the neutropenic episode but also by increasing the anti-infectious capacity of myeloid blood cells.

Why it is important to do this review

An effective prophylaxis of FN during chemotherapy would ideally decrease infection-related morbidity and mortality without the need for dose reductions or delays of chemotherapy. There is evidence that CSFs might be effective agents to prevent FN in cancer patients receiving chemotherapy, but the debate on the best prevention strategy remains controversial (Herbst 2009; Kuderer 2006). Current guidelines recommend the prophylactic use of CSF in cancer chemotherapies with an estimated risk of FN of about

20% and in patients who have already experienced a febrile neutropenic episode (Aapro 2011; Crawford 2007; Crawford 2010; Smith 2006). However, observational data suggest that the utilization of CSFs does not comply with current guidelines (Ramsey 2010). Considering the prevalence of breast cancer, the high costs of infectious complications after chemotherapy and of CSF themselves, and the fact that there is no systematically synthesized evidence from randomized controlled trials (RCTs) concerning the efficacy and safety of G-CSFs and GM-CSFs in breast cancer, a systematic review and meta-analysis on this topic are justified.

OBJECTIVES

To identify, assess, meta-analyze and summarize the evidence concerning the efficacy and safety of primary prophylactic CSFs (G-CSFs or GM-CSFs) compared to placebo or no treatment for the prevention of FN, early mortality and infection-related mortality in patients with breast cancer undergoing chemotherapy.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs that compared the use of any kind of either G-CSFs or GM-CSFs versus no treatment or placebo for the prevention of neutropenia and neutropenia-related complications in patients with breast cancer undergoing chemotherapy.

Types of participants

Patients with breast cancer at any stage of disease undergoing treatment with any type and dosage of chemotherapy who were at risk of experiencing FN or neutropenia.

Types of interventions

The intervention group received any kind of either G-CSF or GM-CSF at any administered dosage as primary prophylaxis during each cycle of a standard non-myeloablative chemotherapy prior to the onset of neutropenia in the treatment of breast cancer.

The control group had to receive the identical chemotherapy regimen as the intervention group and a placebo or no treatment was given instead of G-CSF or GM-CSF.

If studies assessed primary CSF prophylaxis in the intervention arms and allowed secondary CSF prophylaxis in control arms in subsequent cycles, studies were included but we used only outcome data of cycle one (except for hard outcomes: mortality data) in our meta-analysis.

We excluded trials investigating the sequential administration of G-CSF or GM-CSF or their administration as secondary prophylaxis. We also excluded trials in which CSFs were administered before chemotherapy in order to induce a state of hematopoietic stem-cell arrest (i.e. priming).

Types of outcome measures

Primary outcomes

- Proportion of patients with FN.
- Duration of FN (definition of FN is described for each study).
- Early mortality (mortality during the study).
- Infection-related mortality (during the study).

Secondary outcomes

- Proportion of patients with neutropenia.
- Duration of neutropenia (definition of neutropenia is described for each study).
- Proportion of patients being hospitalized or treated, or both, with antibiotics because of FN.
- Duration of hospitalization and antibiotic treatment.
- Administration of chemotherapy (e.g. number of dose delays or dose reductions, relative dose intensity).
- Incidence of CSF-related adverse effects (e.g. bone pain and injection-site reaction).

Search methods for identification of studies

See: Breast Cancer Group methods used in reviews.

Electronic searches

Deutsches Institut für Medizinische Dokumentation und Information (DIMDI)

We searched the following databases in DIMDI (8 August 2011): Deutsche Ärzteblatt, Global Health, BIOSIS, AMED, CCMED, the Cochrane Central Register of Controlled Trials (CENTRAL), Database of Reviews of Abstracts of Effects, Cochrane Database of Systematic Reviews, EMBASE, EMBASE Alert, Hogrefe Verlagsdatenbank und Volltexte, SciSearch, Krause & Pachernegg Verlagsdatenbank, Karger Verlagsdatenbank, MEDLINE, MEDIKAT, NHS Economic Evaluation database, Thieme Verlagsdatenbank and Thieme Verlagsdatenbank PrePrint. The corresponding search strategy can be seen in Appendix 1. We placed no language restrictions.

Gray literature

For ongoing trials, we searched the ClinicalTrials.gov (clinicaltrials.gov) and the World Health Organization's International Clinical Trials Registry Platform (WHO ICTRP) for technical or research reports, doctoral dissertations and conference papers. We accessed OpenGrey.eu (August 2011). The search strategies used on these databases are in Appendix 2.

Chinese databases

One review author (JPL) conducted searches on three Chinese medical databases (VIP, CNKI and CBM; accessed September 2011). Translations of the trials of interest published in Chinese were conducted by the same review author. The corresponding search strategy can be seen in Appendix 3.

Searching other resources

References from published studies

We screened the reference lists of all located studies for eligible trials by titles first and thereafter screened abstracts of studies of possible interest. Where possible, we obtained a copy of the full article for each reference reporting a potentially eligible trial. Where this was not possible, we attempted to contact the authors to provide additional information. We did not impose language restrictions. Studies that could be excluded after reading the full article were labeled as excluded trials and reasons for exclusion were stated in the Characteristics of excluded studies section.

Unpublished literature

We tried to identify unpublished or ongoing trials through correspondence with experts in the field. We did not impose language restrictions.

Data collection and analysis

Selection of studies

All titles, study information and abstracts retrieved from the electronic searches were downloaded to a reference management database. After the removal of duplicates, screening of the title, abstract and full-text was performed independently by at least two review authors (PR, SM, MH, JL). Assessment for eligibility of the full texts of all potentially relevant references was carried out using an eligibility form that contained the following questions:

- Was the study described as randomized?
- Were the participants being treated with chemotherapy for breast cancer?
- Did patients in the study arms of interest receive the same chemotherapy?
- Were patients of at least one arm given CSFs (the factors include G-CSF or GM-CSF)?
- Did patients of at least one arm receive placebo or no treatment instead of CSF?
- Did the study report at least one of the outcome measures defined in the protocol (see "Types of outcome measures")?

All studies that fulfilled all of the aforementioned criteria were included. In case of disagreement between two review authors, a third review author was consulted.

Data extraction and management

Data extraction

Two review authors (PR, SM) independently extracted data on the characteristics of patients and interventions, study quality components and outcomes onto a data extraction form especially developed for the review. We resolved differences by discussion or by appeal to a third review author (MH), if necessary. We accounted for both clinical and methodological differences of the individual trials. Data for meta-analysis were either extracted from the original publications of the included trials or from other published versions of the trials or were used from additional information that trial authors provided.

Assessment of risk of bias in included studies

We applied the guidelines delineated in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) for the judgment of risk of bias. They were applied according to the following six domains:

- sequence generation;
- allocation concealment;
- blinding of participants, personnel and outcome assessors;
- incomplete outcome data;
- selective outcome reporting; and
- other sources of bias.

When the retrieved information was not available, we contacted the authors of the trial publications to provide the information.

Furthermore, we assessed the quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Higgins 2011).

Measures of treatment effect

The decision on whether or not to combine the results of the included studies in a meta-analysis depended on the similarity of trial characteristics and the number of trials reporting on each outcome. For dichotomous variables, we calculated individual and

pooled statistics as risk ratios (RR) with 95% confidence intervals (CI). In the case where we obtained significant results in our meta-analysis, we calculated the number needed to treat for an additional beneficial outcome (NNTB) and absolute risk reduction (ARR) using a 2 × 2 table (www.ebem.org/nntcalculator.html).

Assessment of heterogeneity

We assessed the heterogeneity of treatment effect between trials by visual inspection of the forest plots, and by using the standard Chi ^{2} test with a significance level of 0.1. We also examined heterogeneity using the I^2 statistic and used thresholds for the interpretation according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). When we detected heterogeneity, we sought reasons for it by examining clinical and methodological characteristics of the individual study and considered the appropriateness of reporting a pooled estimate. Heterogeneity was categorized into four groups depending on the I^2 (Higgins 2011):

- 0% to 30%: low;
- 30% to 50%: moderate;
- 50% to 75%: substantial; and
- 75% to 100%: considerable heterogeneity.

Data synthesis

The study data were pooled using a fixed-effect model. A priori, we assumed only one true estimate and low levels of heterogeneity for all outcomes. In cases where we detected substantial or considerable heterogeneity that could not be declared by specific instances, we used a random-effects model for the respective outcome.

Subgroup analysis and investigation of heterogeneity

We performed subgroup analyses only if one of the outcome parameters demonstrated statistically significant differences between treatment groups and we regarded all subgroup analyses as hypothesis-generating. Where possible, we explored the impact of the type of CSF and the duration of CSF administration (either only in cycle one or across all delivered cycles) on outcomes in a subgroup analysis.

Sensitivity analysis

In general we abandoned sensitivity or post-hoc analysis but where necessary we performed sensitivity analysis owing to moderate to considerable heterogeneity among studies in the meta-analysis.

RESULTS

Description of studies

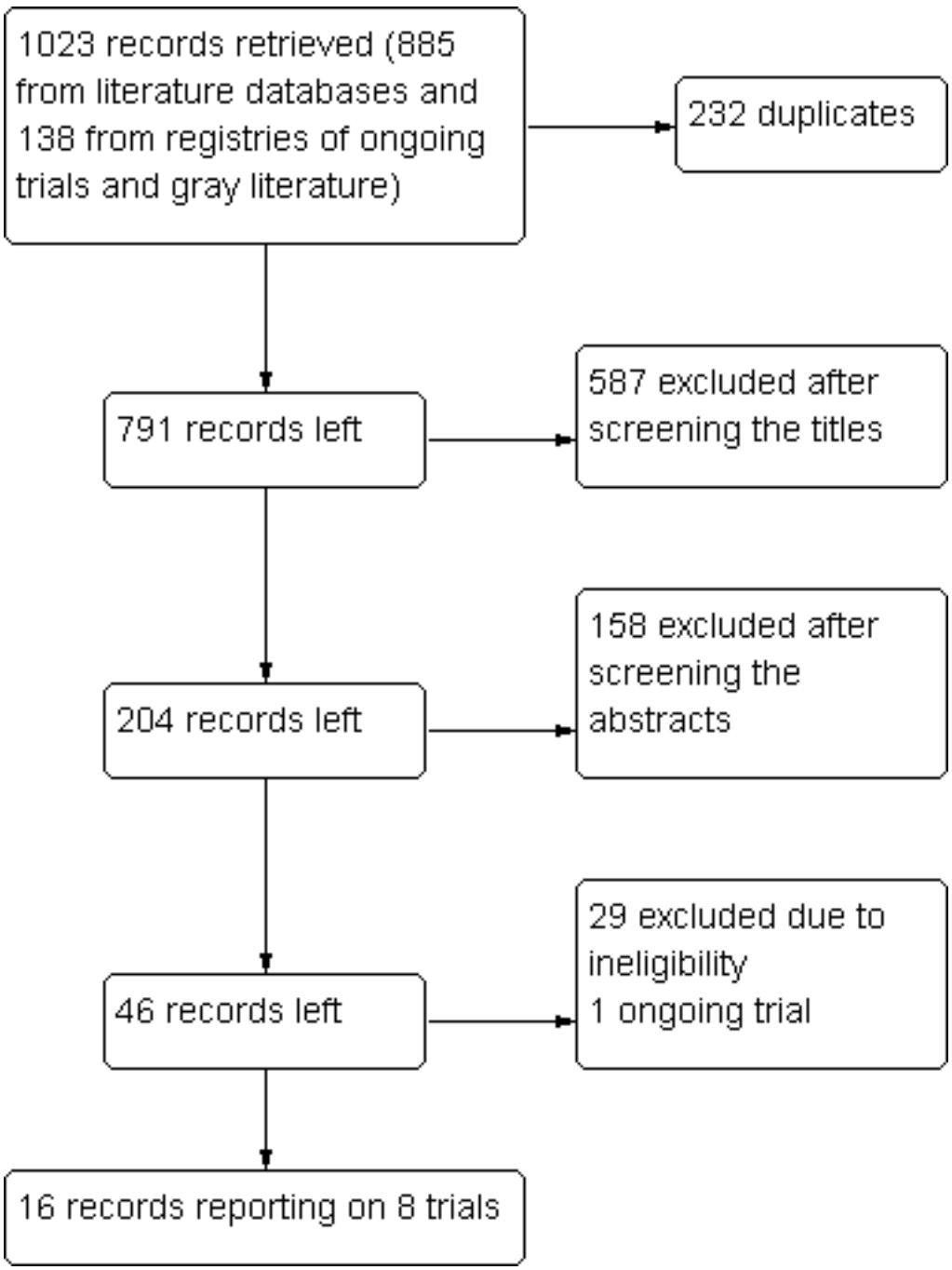
See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

The search strategy identified a total of 1023 citations from which we removed 232 duplicates. In total, screening of the titles and abstracts identified 46 potentially eligible citations. The full-text screening of the 46 publications identified 16 articles that pertained to eight eligible RCTs (Figure 1).

The agreement between review authors for study eligibility was excellent (kappa > 0.9). Reasons for the exclusion of studies are described in the Characteristics of excluded studies table.

Figure 1. Study flow diagram.



Included studies

Eight trials were included in the review (Chevallier 1995; Del Giglio 2008; Hansen 1995; Jones 1996; Muhonen 1996; Papaldo 2003; Romieu 2007; Vogel 2005) and study details are shown in the Characteristics of included studies table. Two trials were conducted in France (Chevallier 1995; Romieu 2007) and one of each in the US (Jones 1996), Denmark (Hansen 1995), Italy (Papaldo 2003), Brazil (Del Giglio 2008) and Finland (Muhonen 1996). Six trials were multicenter studies (Chevallier 1995; Del Giglio 2008; Muhonen 1996; Papaldo 2003; Romieu 2007; Vogel 2005) and Vogel 2005 and Del Giglio 2008 were multinational studies. In addition to the original publication (Papaldo 2003), four papers reported further on this study (Di Cosimo 2005; Papaldo 2004; Papaldo 2005; Papaldo 2006). Data concerning economic outcomes and a 10-year follow-up of Chevallier 1995 was published by Mapelli 1994 and Veyret 2006. Brugger 2009 presented further data of Romieu 2007. Sharma 2004 is a summary of the main findings of Vogel 2005. All study authors were contacted for additional information; however, only two authors kindly provided additional data (Hansen 1995; Papaldo 2003).

Participants

A total of 2156 adult patients (2148 women; eight men) were included in the eight studies (range: 20 to 928; mean: 270; median: 131). The age of the patients ranged from 18 to 78 years and the mean age was approximately 50 years. Romieu 2007 only included patients older than 65 years.

Treatment situations

Three studies treated patients with localized stages and adjuvant chemotherapies after surgery (Jones 1996; Papaldo 2003; Romieu 2007), one with inflammatory breast cancers and neoadjuvant chemotherapy before surgery (Chevallier 1995) and four with metastatic diseases and palliative chemotherapies (Del Giglio 2008; Hansen 1995, Muhonen 1996, Vogel 2005; for details of used chemotherapy regimens see Table 1).

Intervention and control treatments

Six trials used G-CSF: one trial compared lenograstim with placebo (Chevallier 1995), two trials compared pegfilgrastim with placebo (Romieu 2007; Vogel 2005), two trials used filgrastim compared with no treatment (Muhonen 1996; Papaldo 2003) and one trial used a biosimilar filgrastim (non-glycosylated r-metHuG-CSF) compared with filgrastim and with no treatment (Del Giglio 2008).

Two trials used GM-CSF: one trial compared sargramostim with placebo (Jones 1996) and one trial compared GM-CSF with no treatment (Hansen 1995). For details of applied type of CSF refer to Table 2.

Study designs

In all eight studies, patients were treated in parallel designs. Six studies were made up of two study groups, one study was made up of three groups, one study was made up of four groups. All studies included at least four chemotherapy cycles up to a maximum of six cycles. Three studies used true double-blind designs (Chevallier 1995; Jones 1996; Vogel 2005) and in four studies, patients of the control groups were treated with placebo (Chevallier 1995; Del Giglio 2008; Jones 1996; Vogel 2005).

In Jones 1996, Romieu 2007 and Vogel 2005, all patients developing an event of FN at any time during the study were treated with CSFs in all subsequent cycles. Del Giglio 2008 dismantled the control group after cycle one and all patients of this group received the study drug in subsequent cycles. Romieu 2007 compared primary and secondary prophylaxis of pegfilgrastim, and patients who developed FN in the control group in cycle one received pegfilgrastim in all following cycles.

Outcomes

Two trials (Jones 1996; Vogel 2005) described the number of patients with FN as the primary outcome. The six remaining trials reported different primary outcomes: duration of grade IV neutropenia (Chevallier 1995; Del Giglio 2008; Jones 1996), number of neutropenic events (Romieu 2007), disease-free survival (DFS; Papaldo 2003) and duration of severe neutropenia (Hansen 1995). Trial authors' definitions and measurements of outcomes varied considerably (see Table 3).

Febrile neutropenia

All but one study (Muhonen 1996) provided data concerning FN. Six studies reported on the rates of patients developing FN (Chevallier 1995; Del Giglio 2008; Jones 1996; Papaldo 2003; Romieu 2007; Vogel 2005), one study reported on the number of febrile episodes (Papaldo 2003) and one study (Hansen 1995) reported the duration of FN events in days.

Early mortality and infection-related mortality

Four studies reported data on all-cause mortality (Del Giglio 2008; Jones 1996; Romieu 2007; Vogel 2005) and five studies reported on infection-related mortality during the study (Chevallier 1995;

Del Giglio 2008; Jones 1996; Romieu 2007; Vogel 2005). In those studies where the authors did not report on mortality, we assumed that no deaths had occurred.

Severe neutropenia

Four trials reported on the rates of patients with severe (WHO grade IV) neutropenia (Jones 1996; Muhonen 1996; Papaldo 2003; Romieu 2007).

Infections

Three studies reported on the incidence of infections (Chevallier 1995; Muhonen 1996; Romieu 2007). Chevallier 1995 distinguished between fever of unknown origin and clinically or microbiologically documented infections. Romieu 2007 and Muhonen 1996 stated only the number of patients with infections.

Hospitalization

Two trials reported on the rate of patients being hospitalized because of FN (Jones 1996; Vogel 2005), while three trials reported on the duration of hospitalization for any reason (Chevallier 1995; Hansen 1995; Muhonen 1996).

Use of antibiotics

Four trials reported on the rates of patients treated with intravenous (i.v.) antibiotics because of FN (Hansen 1995; Jones 1996; Papaldo 2003; Vogel 2005) and two trials on the duration of treatment with i.v. antibiotics (Chevallier 1995; Hansen 1995).

Administration of chemotherapy

Four studies reported the percentage or the number of patients who received the planned chemotherapy doses at scheduled times and doses (Chevallier 1995; Papaldo 2003; Romieu 2007; Vogel 2005). Three studies (Chevallier 1995; Hansen 1995; Papaldo 2003) reported the number of patients who received all planned cycles. Two further studies reported dose reductions of single chemotherapy agents (Muhonen 1996; Jones 1996); however, the reporting quality was so low that the data could not be used.

Adverse events

All studies reported short-term adverse events related to CSF use. The most common were injection-site reactions and bone pain. We extracted data concerning injection-site reactions from two studies (Chevallier 1995; Jones 1996) and bone pain from three studies (Chevallier 1995; Muhonen 1996; Papaldo 2003), which reported rates for both study arms. Late-term adverse events were not reported in any of the included trials.

Conflicts of interests

Three trials explicitly declared possible conflicts of interest (Del Giglio 2008; Romieu 2007; Vogel 2005) and five trials acknowledged assistance from the pharmaceutical industry and supply of study medication (Chevallier 1995; Del Giglio 2008; Muhonen 1996; Romieu 2007; Vogel 2005). In the Vogel 2005 trial, six out of the eight authors were affiliated with the manufacturer of the interventional drug. No details about the source of the study medication were provided in Hansen 1995, Jones 1996 and Papaldo 2003.

Excluded studies

Trials that were first considered to be of possible relevance but were subsequently excluded can be viewed at the Characteristics of excluded studies table. The main reasons for excluding trials were different chemotherapy regimens between study groups and missing control groups. No ongoing studies or studies awaiting classification were suitable for inclusion at the time point when we conducted the review.

Risk of bias in included studies

The quality of the included studies and their risk of bias were assessed separately for the different outcomes of primary interest (FN and early/infection-related mortality). The studies are grouped below by the grades of risk of bias.

The included studies were judged as having the following risk of bias concerning FN:

- low: Chevallier 1995;Jones 1996;
- moderate: Del Giglio 2008;Vogel 2005;
- moderate to high: Papaldo 2003; Romieu 2007;
- high: Hansen 1995.

Muhonen 1996 did not report on this outcome. The funnel plot of the six studies reporting the numbers of patients developing at least one event of FN suggested potential publication bias owing to missing studies reporting results to the right-hand side of the drawn effect-size. Assessing funnel plots of outcomes other than FN was impossible owing to the small number of studies.

The included studies were further judged as having the following risk of bias concerning early mortality and infection-related mortality:

- low: Chevallier 1995;Jones 1996;
- low to moderate: Del Giglio 2008;Romieu 2007;
- moderate: Hansen 1995;Muhonen 1996; Papaldo 2003; Vogel 2005.

Overall, the reasons for higher grades of risk of bias were because of inadequate reporting of the methods used for random allocation, unblinded study designs, unbalanced risk factors for the outcome of interest, inadequate definitions and measurements of outcomes (Table 3), different supportive treatment between groups and small sample sizes. To allow for comparisons, we assessed the quality of

each study using the Jadad scale, which resulted in an average score of 2.3 of a maximum of 5 (range: 1 to 4) and the Delphi scale with an average score of 4.6 of a maximum of 7 (range: 4 to 7).
For the risk of bias of the included studies in detail refer to the Characteristics of included studies, Figure 2 and Figure 3.

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

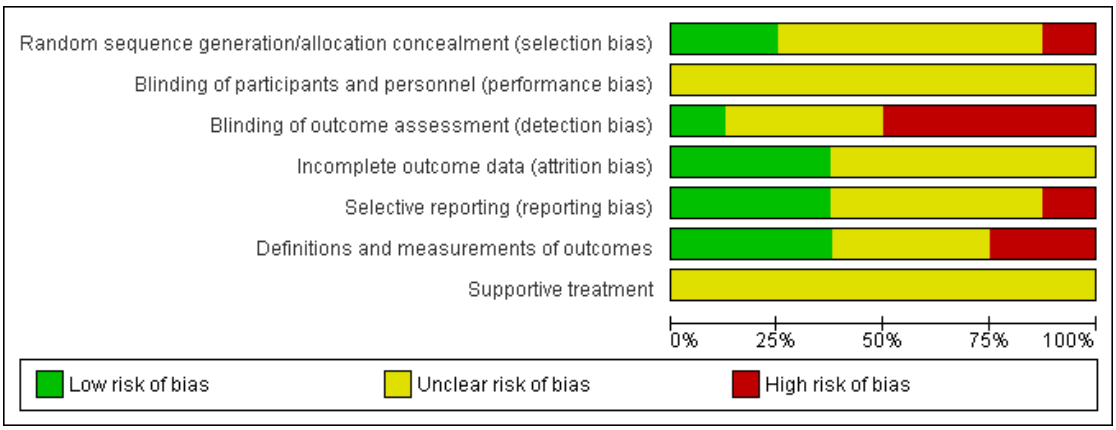
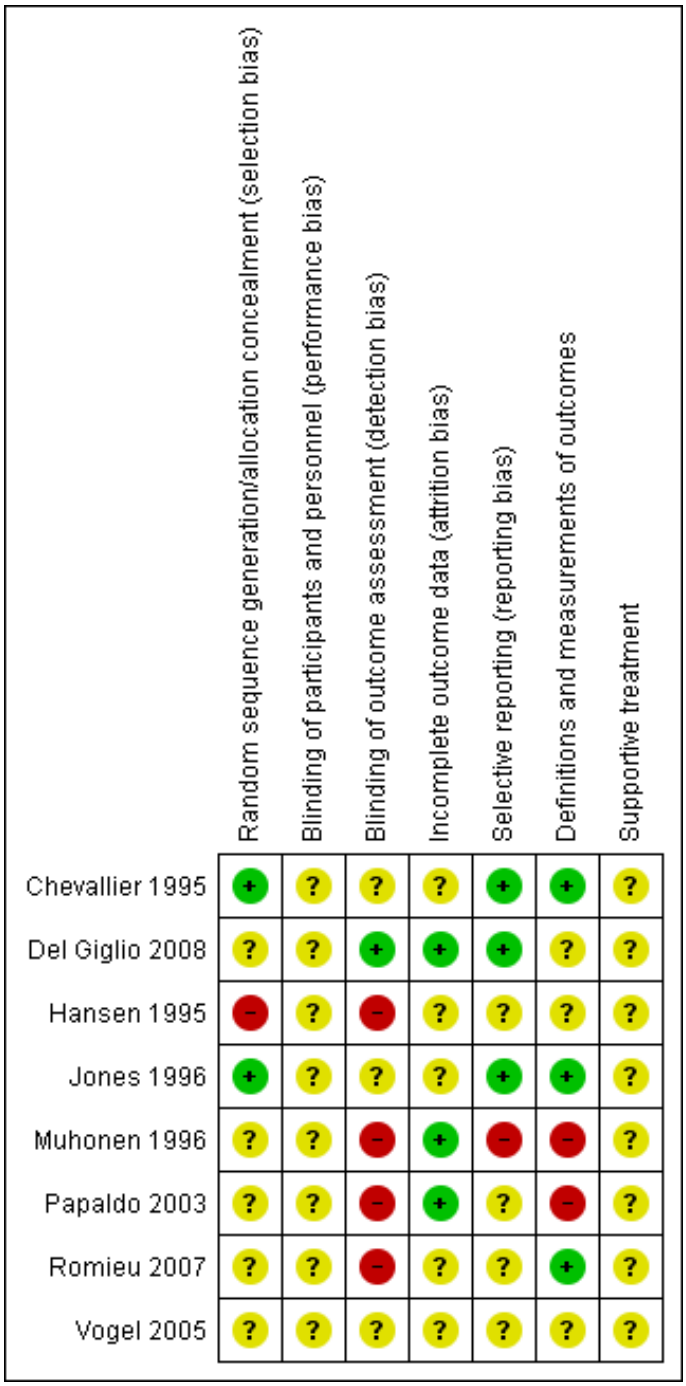


Figure 3. 'Risk of bias' summary: review authors' judgments about each 'Risk of bias' item for each included study.



Effects of interventions

See: **Summary of findings for the main comparison** Prevention of chemotherapy-induced FN in breast cancer patients - primary outcomes; **Summary of findings 2** Prevention of chemotherapy-induced FN in breast cancer patients - secondary outcomes

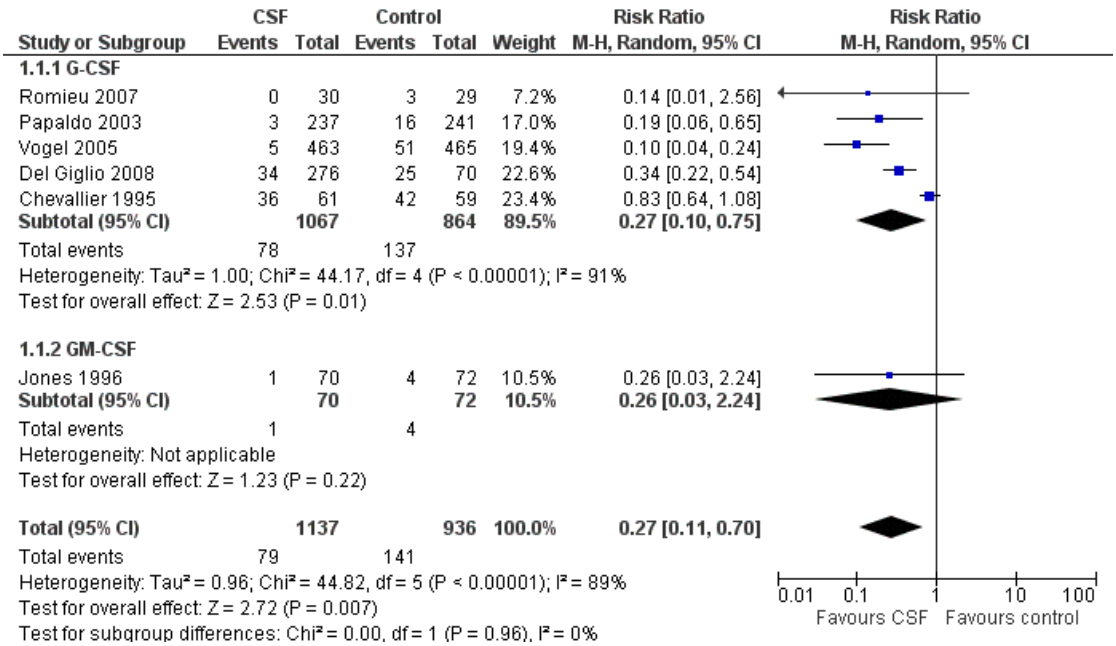
For the analyses, we used first-cycle data from Jones 1996, Romieu 2007 and Vogel 2005. In these three studies, CSFs were applied as secondary prophylaxis in case of developing a febrile neutropenic event in patients of the control groups from cycle two and did not met the inclusion criteria in these cycles. Data of cycles two to four of Del Giglio 2008 could not be used for analysis because the control group was dissolved after the first cycle in this study. We used cumulated data across all cycles of the four remaining trials (Chevallier 1995; Hansen 1995; Muhonen 1996; Papaldo 2003).

Febrile neutropenia

Number of patients

In six studies, a total of 79 of 1137 patients in the intervention groups and 141 of 936 patients in the control groups developed at least one episode of FN (Chevallier 1995; Del Giglio 2008; Jones 1996; Papaldo 2003; Romieu 2007; Vogel 2005; Table 4). The pooled risk of FN was significantly reduced in CSF-treated patients (RR 0.27; 95% CI 0.11 to 0.70; Analysis 1.1; Figure 4). The percentage of the variability in the effect estimates owing to heterogeneity rather than by chance was substantial (I^2 = 89%; NNTB 12; ARR 0.08). When we analyzed the data without Chevallier 1995, who defined FN in a broader way, heterogeneity was reduced (I^2 = 50%). There was no heterogeneity (I^2 = 0%) when we excluded Vogel 2005 and Romieu 2007 (two studies that used pegfilgrastim). The treatment benefit of the filgrastim-treated patients in the three remaining studies remained significant (RR 0.32; 95% CI 0.21 to 0.48).

Figure 4. Forest plot of comparison: 1 Primary outcomes, outcome: 1.1 number of patients with at least one event of FN during the study period.



Subgroup analyses

First-cycle data and cumulated data across all chemotherapy cycles

Two studies reported on cumulated FN rates across all cycles.

Thirty-nine of 298 patients in the intervention groups and 58 of 300 patients in the control groups had at least one episode of FN (Chevallier 1995; Papaldo 2003). The pooled RR was 0.44 and not significant (95% CI 0.09 to 2.24) with substantial heterogeneity (I^2 = 86%; Analysis 1.2). Four studies reported on FN rates during the first cycle of chemotherapy. Forty of 839 patients in the intervention groups and 83 of 636 patients in the control groups developed FN (Del Giglio 2008; Jones 1996; Romieu 2007; Vogel 2005). The risk of FN was significantly reduced in CSF-treated patients (RR 0.20; 95% CI 0.08 to 0.52) with substantial heterogeneity (I^2 = 61%; Analysis 1.3). Heterogeneity disappeared when two pegfilgrastim studies were excluded (Romieu 2007; Vogel 2005; I^2 = 0%), while the RR remained significant (RR 0.34; 95% CI 0.22 to 0.53). Both pegfilgrastim studies also remained free from heterogeneity (I^2 = 0%) and showed significant treatment benefits (RR 0.10; 95% CI 0.04 to 0.24).

G-CSF and GM-CSF

In the five G-CSF studies, 78 of 1067 patients in the intervention groups and 137 of 864 patients in the control groups developed FN (RR 0.23; 95% CI 0.11 to 0.46; Chevallier 1995; Del Giglio 2008; Papaldo 2003; Romieu 2007; Vogel 2005) and heterogeneity was substantial (I^2 = 62%). The GM-CSF study reported one of 70 patients in the interventional groups and four of 72 patients in the control groups with FN and this did not result in a significant treatment benefit for GM-CSF-treated patients (RR 0.25; 95% CI 0.03 to 2.26; Jones 1996).

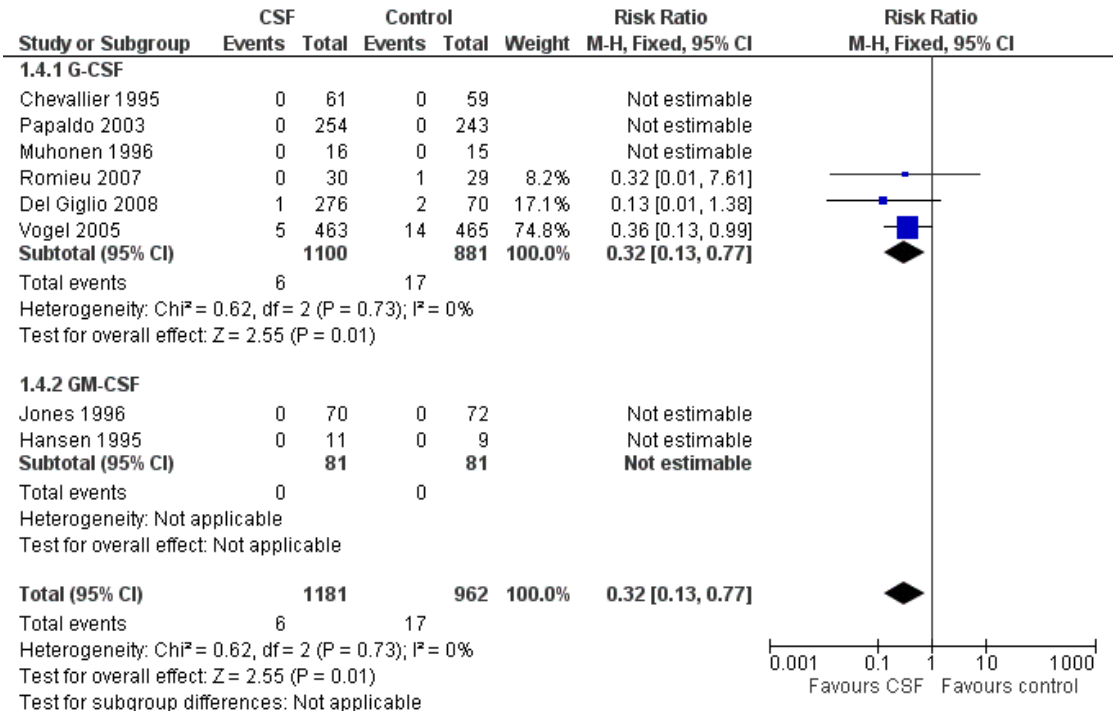
Duration

Only one study (Hansen 1995) reported on the duration of febrile neutropenic events and reported a non-significant difference of one day between the intervention group (median: four days) and the control group (median: five days) across all cycles.

Early mortality

In all eight studies, six of 1181 patients in the intervention groups and 17 of 962 patients in the control groups died during the study (Chevallier 1995; Del Giglio 2008; Hansen 1995; Jones 1996; Muhonen 1996; Papaldo 2003; Romieu 2007; Vogel 2005). Causes of death are listed in Table 5. The early mortality risk was significantly lower in CSF-treated patients (RR 0.32; 95% CI 0.13 to 0.77) without heterogeneity among the trials (I^2 = 0%; NNTB 79; ARR 0.01; Analysis 1.4; Figure 5). The RR of early mortality was mainly affected by the large study of Vogel 2005, which reported five versus 14 deaths in the control and intervention group, respectively. The significance of the difference disappeared when Vogel 2005 was excluded from analysis (RR 0.19; 95% CI 0.03 to 1.24).

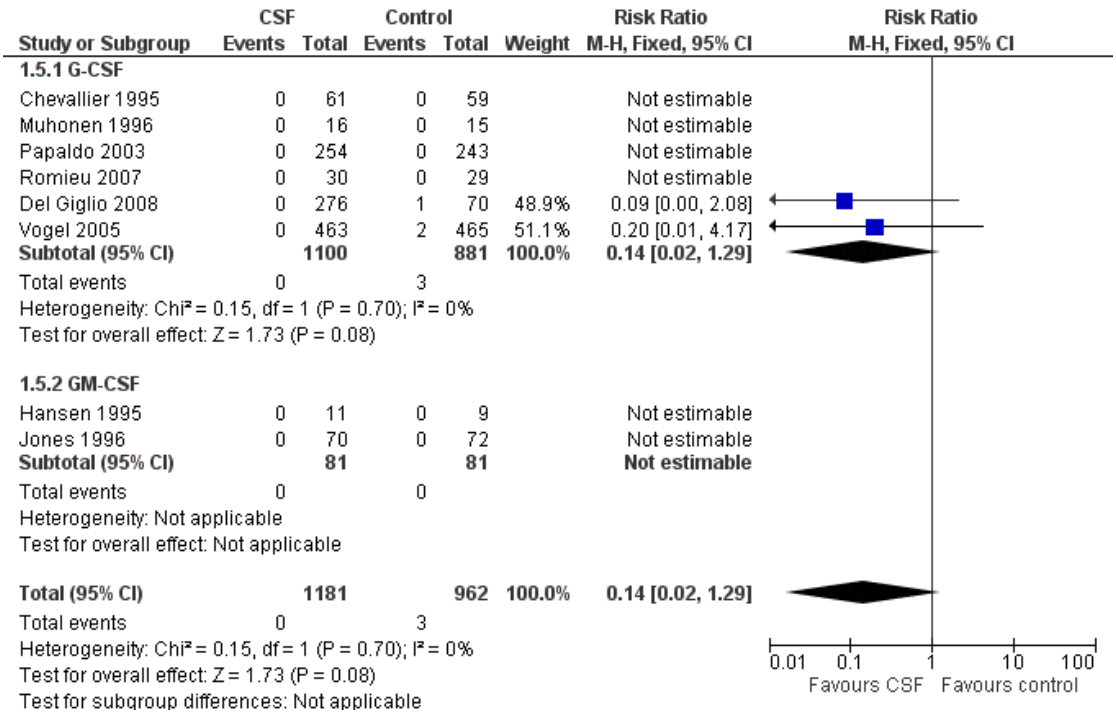
Figure 5. Forest plot of comparison: 1 Primary outcomes, outcome: 1.4 Early mortality during the study period.



Infection-related mortality

In all eight studies, none of the 1181 patients in the intervention groups and three of 962 patients in the control groups died of infections. Two of the three deaths occurred in Vogel 2005 and one in Del Giglio 2008. Causes of deaths are listed in Table 6. The differences in the risk of dying from infection were not significant (RR 0.14; 95% CI 0.02 to 1.29; Analysis 1.5; Figure 6). The results were homogeneous (I^2 = 0%; Analysis 1.5).

Figure 6. Forest plot of comparison: 1 Primary outcomes, outcome: 1.5 Infection-related mortality.



Neutropenia

Number of patients

In four studies, a total of 83 of 353 patients in the intervention groups and 191 of 359 patients in the control groups developed at least one episode of severe (WHO grade IV) neutropenia (N4) (Jones 1996; Muhonen 1996; Papaldo 2003; Romieu 2007 Table 4). The risk of N4 was not significantly reduced in CSF-treated patients (RR 0.44; 95% CI 0.17 to 1.18) with considerable heterogeneity among the studies (I^2 = 96%; Analysis 2.1). Heterogeneity could not be further reduced.

Subgroup analyses

First-cycle data and cumulated data across all chemotherapy cycles

We used data from Muhonen 1996 and Papaldo 2003 who reported rates of patients with neutropenia across all cycles of chemotherapy. Seventeen of the 253 patients in the intervention group and 113 of 258 patients in the control group developed at least one neutropenic event that was significant (RR 0.19; 95% CI 0.08 to 0.45; Analysis 2.2). In two studies (Jones 1996; Romieu 2007) that reported the rates of patients who developed at least one neutropenic event during cycle one, 66 of 100 patients in the intervention group and 78 of 101 patients in the control group developed at least one neutropenic event. The meta-analysis showed no significant benefits for CSF-treated patients (RR 0.89; 95% CI 0.66 to 0.21; Analysis 2.3). Both subgroup analyses were of substantial heterogeneity (I^2 = 0.64 and I^2 = 0.63, respectively).

G-CSF and GM-CSF

In the three studies (Muhonen 1996; Papaldo 2003; Romieu 2007) applying G-CSFs, 40 out of 283 patients in the intervention group and 134 of 287 patients in the control group developed at least one neutropenic event. The result was not significant (RR 0.36; 95% CI 0.05 to 2.44) and had considerable heterogeneity (I^2 = 97%; Analysis 2.1). Jones 1996 who applied GM-CSFs showed a significant benefit for patients in the intervention group (RR 0.78; 95% CI 0.62 to 0.97).

Duration

A pooled analysis of the duration of N4 could not be carried out because trial authors did not report the required details (e.g. standard deviations). However, all studies that investigated the duration of N4 reported that, on average, N4 lasted two days longer in the control groups compared to the CSF groups (Chevallier 1995; Del Giglio 2008; Hansen 1995; Jones 1996; Romieu 2007 Table 7).

Infections

In three studies, 55 of 107 patients in the intervention groups and 62 of 103 patients in the control groups experienced at least one infectious complication (Chevallier 1995; Muhonen 1996; Romieu 2007; Table 8). The RR was 0.86 (95% CI 0.72 to 1.02) without heterogeneity among the trials (I^2 = 0%; Analysis 2.4).

Hospitalization

In four studies, a total of six of 574 patients in the intervention groups and 50 of 575 patients in the control groups were admitted to hospital on at least one occasion (Hansen 1995; Jones 1996; Romieu 2007; Vogel 2005; Table 9). The risk for hospitalization was significantly reduced in CSF-treated patients (RR 0.14; 95% CI 0.06 to 0.30) without heterogeneity among the trials (I^2 = 0%; NNTB 13; ARR 0.08; Analysis 2.5).

Subgroup analyses

First-cycle data and cumulated data across all chemotherapy cycles

We only used data from Hansen 1995 who reported rates of patients hospitalized across all cycles of chemotherapy. None of the 11 patients in the intervention groups and one of nine patients in the control groups were admitted to hospital on at least one occasion, which was not significant (RR 0.28; 95% CI 0.01 to 6.10; Analysis 2.6). In three studies that reported the rates of patients hospitalized during cycle one, six of 563 patients in the intervention groups and 49 of 566 patients in the control groups were admitted to hospital. The meta-analysis showed significant benefits for CSF-treated patients (RR 0.13; 95% CI 0.06 to 0.30) and the results were homogeneous (I^2 = 0%; Jones 1996; Romieu 2007 Vogel 2005).

G-CSF and GM-CSF

In the two studies applying G-CSF, five of the 493 patients in the intervention groups and 45 of 494 patients in the control groups were hospitalized (mainly for FN, severe neutropenia or infections). The risk for being hospitalized was significantly lower in the CSF groups (RR 0.12; 95% CI 0.05 to 0.29) and the results were homogeneous (I^2 = 0%; Romieu 2007; Vogel 2005; Analysis 2.5). In the two studies applying GM-CSF, one out of 81 patients in the intervention groups and five of 81 patients in the control groups were admitted to hospitals. The difference was not significant (RR 0.26; 95% CI 0.04 to 1.56; Hansen 1995; Jones 1996) and there was no heterogeneity (I^2 = 0%).

Use of intravenous antibiotics

In four studies, 22 of 781 patients in the intervention groups and 65 of 787 patients in the control groups were treated at least once with i.v. antibiotics (Hansen 1995; Jones 1996; Papaldo 2003; Vogel 2005; Table 9). The risk for being treated with i.v. antibiotics was significantly lower in CSF-treated patients (RR 0.35; 95% CI 0.22 to 0.55) with low heterogeneity among the trials (I^2 = 19%; NNTB 18; ARR 0.05; Analysis 2.8).

Subgroup analyses

First-cycle data and cumulated data across all chemotherapy cycles

In two studies, 16 of 248 patients in the intervention groups and 33 of 250 patients received i.v. antibiotics during all cycles of chemotherapy (Hansen 1995; Papaldo 2003). The pooled risk for antibiotic treatment was also significantly reduced (RR 0.50; 95% CI 0.28 to 0.87) without heterogeneity (I^2 = 0%; Analysis 2.9).
In two studies, six of 533 patients in the intervention groups and 32 of 537 patients in the control groups received i.v. antibiotics in the first cycle of chemotherapy (Jones 1996; Vogel 2005). The pooled risk for being treated was lower in the CSF group albeit not significant (RR 0.40; 95% CI 0.03 to 4.77) with considerable heterogeneity between the trials (I^2 = 96%; Analysis 2.10).
The pooled risk for being treated with i.v. antibiotics was significantly lower in the two studies applying G-CSF (RR 0.35; 95% CI 0.22 to 0.57; Papaldo 2003; Vogel 2005) with substantial heterogeneity between the two trials (I^2 = 72%). In the two studies applying GM-CSF, there was no significant difference in the risks (RR 0.26; 95% CI 0.04 to 1.56) with no heterogeneity (I^2 = 0%; Hansen 1995; Jones 1996).

Administration of chemotherapy

In four studies, 674 out of 794 patients in the intervention groups and 647 out of 794 patients in the control groups received the planned chemotherapy cycles at scheduled times and doses (Chevallier 1995; Papaldo 2003; Romieu 2007 Vogel 2005; Table 10). The RR was 1.05 (95% CI 0.97 to 1.13) with substantial heterogeneity (I^2 = 61%; Analysis 2.11). There were no GM-CSF studies in the analysis.

Adverse events

Bone pain

Two studies with a total of 151 patients reported the number of patients with bone pain in both study arms (Chevallier 1995; Muhonen 1996). Papaldo 2003 did not report the number of patients with bone pain in the control group and therefore could not be considered for analysis. The pooled risk (RR) for bone pain was 5.88 for CSF-treated patients (95% CI 2.54 to 13.60) with no heterogeneity (I^2 = 0%; NNTH 3; Table 11 Analysis 2.12).

Injection-site reaction

Two studies with a total of 262 patients reported the number of patients with injection-site reactions (Chevallier 1995; Jones 1996). The pooled risk (RR) for injection-site reaction was 3.59 for CSF-treated patients (95% CI 2.33 to 5.53) with no heterogeneity (I^2 = 0%, NNTH 3; Table 11 Analysis 2.13).

ADDITIONAL SUMMARY OF FINDINGS [*Explanation*]

Prevention of chemotherapy-induced FN in breast cancer patients - secondary outcomes

Patient or population: breast cancer patients undergoing chemotherapy
Settings: randomized controlled trials
Intervention: primary prophylactic G-CSF/GM-CSF

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Primary prophylactic G-CSF/GM-CSF				
Severe neutropenia (WHO grade IV) Rates of patients	**532 per 1000**	**234 per 1000** (192 to 282)	**RR 0.44** (0.17 to 1.18)	712 (4 studies)	⊕⊕⊕◯ **moderate**[1,2]	
Infections Rates of patients	**602 per 1000**	**307 per 1000** (144 to 662)	**RR 0.86** (0.72 to 1.02)	210 (3 studies)	⊕⊕◯◯ **low**[2,3]	
Hospitalization Rates of patients	**87 per 1000**	**12 per 1000** (5 to 26)	**RR 0.14** (0.06 to 0.3)	1149 (4 studies)	⊕⊕◯◯ **low**[2,4]	
Antibiotics (i.v.) Rates of patients	**83 per 1000**	**29 per 1000** (18 to 45)	**RR 0.35** (0.22 to 0.55)	1568 (4 studies)	⊕⊕◯◯ **low**[2,4]	
Chemotherapy Rates of patients who received the planned chemotherapy doses at scheduled times and doses	**815 per 1000**	**856 per 1000** (815 to 888)	**RR 1.05** (0.97 to 1.13)	1588 (4 studies)	⊕⊕◯◯ **low**[2,5]	
Bone pain Rates of patients	**68 per 1000**	**397 per 1000** (172 to 919)	**RR 5.88** (2.54 to 13.6)	388 (3 studies)	⊕⊕⊕◯ **moderate**[2,6]	

Injection-site reaction Rates of patients	**153 per 1000**	**548 per 1000** (356 to 844)	**RR 3.59** (2.33 to 5.53)	262 (2 studies)	⊕⊕⊕○ **moderate**[2,6]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; G-CSF: granulocyte colony-stimulating factors; GM-CSF: granulocyte-macrophage colony-stimulating factors; i.v.: intravenous; RR: risk ratio; WHO: World Health Organization

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

[1] Only four studies reported outcome; no blinded outcome assessment; unclear schedule of outcome measurements.
[2] Studies on average at moderate risk of bias.
[3] Small number of patients in analysis; no blinded outcome assessment; varying definitions of outcome.
[4] Depending outcome (febrile neutropenia); no blinded outcome assessment; varying definitions of outcome.
[5] Influence of differential supportive treatments unclear; varying treatments and settings.
[6] Small number of patients; large effect size; one study with blinded care provision.

DISCUSSION

Summary of main results

This is the first systematic review and meta-analysis that has addressed the evidence for the use of CSFs on the prevention of FN and its complications in patients with breast cancer undergoing chemotherapy. We identified eight RCTs with a total of 2156 patients. The patients were treated with neoadjuvant (one study), adjuvant (three studies) or palliative chemotherapy regimens (four studies). Six studies used G-CSF (three filgrastim, two pegfilgrastim, one lenograstim) and two studies used GM-CSF (one molgramostim and one sargramostim). The majority of studies were judged as being at least at moderate risk of bias.

In our meta-analysis, CSFs significantly reduced the number of patients with FN (RR 0.27; NNTB 12), early mortality (RR 0.32; NNTB 79), the need for hospital care (RR 0.14; NNTB 13) and the application of i.v. antibiotics (RR 0.35; NNTB 18). The duration of FN or severe neutropenic events could not be assessed because of the limited number of studies reporting this outcome or the poor quality of reporting. CSFs frequently caused specific short-term adverse effects like bone pain (RR 5.88; NNTH 3) and injection-site reactions (RR 3.59; NNTH 3) and did not significantly reduce the risk of severe neutropenia, infections and infection-related mortality. The administration of CSFs did not confer better maintenance of chemotherapy regimens at scheduled times and doses.

Overall completeness and applicability of evidence

This review summarized the evidence regarding primary prophylaxis of neutropenia-related complications with CSFs in a variety of settings. The included trials comprised different breast cancer samples (i.e. metastatic disease, adjuvant treatment situations, inflammatory cancers), investigated six different types of CSFs and took place in different countries with different health care systems, thus increasing the generalizability of these results. However, the overall completeness of the review findings is limited and the applicability of evidence restricted owing to the following aspects.

First, more than 40% of the patients included in our analyses came from one study with a moderate risk of bias and the overall number of included studies was small.

Second, most outcomes were investigated insufficiently. For example, fewer than half of the studies applied standard definitions of FN and only one study differentiated the etiology of infections or febrile episodes according to the definitions of the International Immunocompromised Host Society (ICHS). Furthermore, most studies measured body temperature orally in order to detect FN. There is not only clear evidence that the accuracy and reliability of the measurement of body temperature depends on the site and method of measurement but also that oral mucositis can lead to inaccurate estimates when fever is measured orally. Ciuraru et al (Ciuraru 2008) found evidence that chemotherapy-associated mucositis in breast cancer patients increased the oral but not systemic body temperature. They concluded that "mucositis may provide an 'inflammation bias' that could lead to the overuse of antibiotics and growth factors in 20% to 40% of patients with cancer" (Ciuraru 2008). In addition, although there was evidence that the exact timing of blood counts during chemotherapy might optimize G-CSF prophylaxis (Ammann 2002), only three trials reported daily measurement schedules of body temperature and ANCs. Hence, evidence of treatment effects on these outcomes or on depending outcomes (e.g. hospitalization) needs to be interpreted carefully including the non-significant effects on the prevention of severe neutropenia. Moreover, most trials were underpowered to detect effects of CSF treatments on outcomes, which rarely occur during treatment with chemotherapies with low to moderate risk of FN such as infection-related and early mortality.

Third, five of the eight studies reported no deaths and in the remaining three studies, a very small number of events occurred. Nineteen of 23 events were reported in one study and were attributed to disease progression by the authors (Vogel 2005). The reduction of all-cause mortality therefore might be attributed to different risk factors rather than to treatment effects of CSFs.

Fourth, the trials' study populations differed considerably regarding baseline risks of FN and infections. Sensitivity analyses were considered to examine the differential effects of CSFs on different risk populations; however, the analyses were not feasible in the present review, owing to the small number of trials per disease stage or treatment situation. No studies were identified in which the effectiveness of CSFs in breast cancer patients with different risks were compared. Thus, conclusions cannot be drawn regarding differential treatment effects depending on different risks.

Fifth, current guidelines on the use of CSFs during cancer chemotherapy recommend prophylactic CSFs in chemotherapy regimens with a risk of FN of more than 20%. However, only two out of six studies that reported on this outcome had an incidence of FN of more than 20% in the control group (Chevallier 1995; Del Giglio 2008). All other studies had risks in the control groups between 10% and 20% (Jones 1996; Romieu 2007; Vogel 2005) or even below 10% (Papaldo 2003). Therefore, the results of our analyses were based on trials in which CSFs were given to patients of whom many, according to current guidelines, did not qualify for prophylactic administration of CSFs.

Sixth, the application schedules of filgrastim examined in the included trials varied considerably. Del Giglio 2008 scheduled filgrastim treatment 24 hours after chemotherapy, Muhonen 1996 on day four and Papaldo 2003 on day eight. The timing of filgrastim administration post-chemotherapy has profound effects on hematologic recovery. There is evidence that the effectiveness of filgrastim depends on its dose schedule (Crawford 1997) and that beginning on day four to six yielded better hematologic recoveries compared with administration of filgrastim on day eight.

The results of Papaldo 2003 furthermore suggested that not only the beginning of CSF treatment but also a less intense schedule with only two applications of filgrastim (day eight and 12 after chemotherapy) could be as effective as the usually applied constant dosing schedules. Hendler 2011 found possible benefit even for shorter treatment schedules with filgrastim in patients with breast cancer. Therefore, included trials with delayed and longer schedules might have led to an underestimation of the treatment effect. Seventh, several of the chemotherapy regimens in the included studies were either uncommon drug combinations or rarely used in the given schedule for the respective treatment situations (Chevallier 1995; Del Giglio 2008; Hansen 1995; Muhonen 1996; Papaldo 2003).

Finally, current guidelines no longer recommend supportive treatment with GM-CSFs (e.g. Aapro 2011; Crawford 2010), although there is evidence that sargramostim could be a cost-effective alternative to filgrastim or pegfilgrastim in the prevention of FN and related complications (Heaney 2009).

Quality of the evidence

The eight included RCTs differed with regards to their risk of bias and quality of reporting. Only two trials were judged as having only minor deficiencies in methodological quality. The results of all other studies were deemed to be influenced by a certain degree of selection, performance or detection bias owing to unconcealed treatment allocation, lack of blinding of patients and care providers, or unblinded outcome assessments. In addition, the supportive treatments applied for the outcomes of interest (infections, etc.) were not adequately reported and might have individual variations, which would mask or bias the results.

Three trials declared possible conflicts of interest and five trials acknowledged assistance from the pharmaceutical industry and supply of study medication. In the largest trial, six out of the eight trial authors were affiliated with the manufacturer of the interventional drug. It has been shown that studies sponsored by pharmaceutical companies were more likely to have outcomes favoring the sponsor than were studies with other sponsors (Higgins 2011).

Despite our comprehensive search strategy, there might be unpublished trials with non-significant results. We were not able to obtain published protocols for most included trials in this review and thus were not able to judge the risk of selective reporting for these studies reliably.

Potential biases in the review process

This review considered the currently available information on this topic. A comprehensive search of the literature was carried out without any language restrictions and included Chinese databases. It is of note that searches of the gray literature identified a large Italian study that was planned as a four-arm study with two arms investigating a research question related to CSF efficacy and was probably eligible for inclusion in our review. However, those two arms had not been carried out, according to the trial author, and the other two arms had been published in 2005 (Venturini 2005). It is also of note that one large ongoing study awaits assessment (Amgen 2015) and may be included in an update of this review. We contacted all relevant pharmaceutical companies but did not receive any RCT data from them. There is the potential for publication bias, which might be an issue in this review given the virtual non-existence of negative findings that have been published, as demonstrated in the funnel plot of the primary outcome FN.

When pooled analyses were performed for some outcomes, high levels of heterogeneity were found. Heterogeneity appeared to result from differences in outcome definitions and the type of CSF used. We carried out a subgroup analysis for the primary outcome, FN, according to the cycle of chemotherapy in which the FN was recorded (first cycle, all cycles) and the type of CSF (G-CSF, GM-CSF), which suggested a higher preventive effectiveness of CSFs during the first cycle and an advantage for G-CSF. Nevertheless, these analyses included only six trials. Furthermore, we could not perform any further subgroup analyses owing to the lack of data. A meta-analysis of secondary outcomes, such as the duration of neutropenia and hospitalization, could not be carried out since these variables were not given as mean numbers or the trial authors did not report standard deviations.

The findings of all outcomes should be regarded as uncertain because only results from up to six studies were available for the analyses and the results on early mortality and infection-related mortality were mainly based on the Vogel 2005 study, which was judged to have a moderate risk of bias and contributed more than 40% of all patients to the meta-analyses.

Agreements and disagreements with other studies or reviews

There are no published systematic reviews on the effectiveness of CSFs on FN and its complications in patients with breast cancer receiving chemotherapy. Two reviews in the area prior to this review included two of our eight included trials in aggregated analyses with other solid tumors (Kuderer 2007; Sung 2007). Kuderer 2007 was an update of Lyman 2002 with more included studies and was republished in 2011 (Kuderer 2011).

Our findings were that the administration of CSFs helped to prevent events of FN and reduced the need for hospital care, which was in line with the findings from both reviews (Kuderer 2007; Sung 2007). Kuderer 2007 furthermore found a reduction for all-cause mortality during chemotherapy and infection-related mortality across a broad range of different cancers, chemotherapy regimens and baseline risks. We also detected a reduction of early mortality; however, 19 of the 23 fatal events had occurred in only one study and five out of eight studies in this analysis did not report deaths during the study period. In accordance with the find-

ings of Sung 2007 in their subgroup of solid tumors (in which also lymphoma were included), we could not find a reduction in infections or infection-related mortality.
In their analyses of trials with patients with solid tumors, Kuderer 2007 found a higher relative dose intensity of chemotherapy in groups with CSFs. We also found a slightly higher rate of patients in the CSF groups who had received the planned chemotherapy cycles at scheduled times and doses.

AUTHORS' CONCLUSIONS

Implications for practice

In patients with breast cancer receiving chemotherapy, CSFs have shown evidence of benefi t in the prevention of FN. There is evidence, though less reliable, of a decrease of all-cause mortality during chemotherapy and a reduced need for hospital care. No reliable evidence was found for a reduction of infection-related mortality, a higher dose intensity of chemotherapy with CSFs or diminished rates of severe neutropenia and infections. The majority of adverse events reported from CSF use were bone pain and injection-site reactions but no conclusions could be drawn regarding late-term side effects. Most studies included in this review used chemotherapy regimens with FN risks below the threshold of 20% for which the administration of CSF is recommended by current best practice guidelines. No meaningful conclusions could be drawn concerning differential effects between the applied CSF in these clinical settings owing to the small number of trials.

Implications for research

The evidence of benefit found in this review notwithstanding, most of the studies included were of uncertain methodological quality and some of them old and carried out before best practice guidelines were implemented. However, observational data suggest that, based on current guidelines, CSFs are underutilized for chemotherapy regimens with high risk of FN and overutilized for those with low risk (Ramsey 2010). In addition, there are doubts that the current management of FN in patients with breast cancer is cost-effective, even if it follows current best practice guidelines (Trueman 2009). Furthermore, there is evidence that not only CSFs but also antibiotics are successful in reducing infectious complications in cancer patients receiving chemotherapy (Gafter-Gvili 2009; Herbst 2009).

Thus, arguments could be made for clinical trials comparing the efficiency of different supportive treatment strategies in preventing FN and its associated morbidity and mortality after chemotherapy with low and moderate FN risk for breast cancer. Future studies should adhere to adequate concealment of randomization and blinding of the interventions and assessment of outcomes (or both), should report data on all-cause mortality, and provide concise definitions as well as properly timed measurements of the outcomes under study.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Chevallier 1995

Methods	Design: 2-arm, double-blind, placebo-controlled, Phase III trial Follow up: after the induction period, patients were evaluated every 4 months for the first 2 years, biannually for the next 3 years, and once per year thereafter Ethical approval: yes
Participants	No. of patients randomized: 120 No. of patients evaluated: 101 (for tumor response) Stage of cancer: invasive and inflammatory breast cancer (T4d) Demographics: women, age range 23 to 65 years (mean age: 48 years) Setting: multicenter study; France Informed consent: yes (written)
Interventions	CSF intervention: G-CSF: lenograstim, 5 μg/kg/d; d6-15 sc; Control: identical placebo Basic treatment: FEC-HD: 5-fluorouracil 750 mg/m^2 d1-4, epirubicin 35 mg/m^2 d2-4, cyclophosphamide 400 mg/m^2 d2-4); every 21d; 4 cycles; Supportive treatment: antibiotics (i.v. or oral, or both) for treatment of FN (primary or secondary prophylaxis was unclear); antibiotics were given in different schedules and dosages according to 3 predefined categories of infections
Outcomes	Primary outcome measures: duration of neutropenia Secondary outcome measures: incidence of FN; events of FN; ANC profiles; incidence of infections; hospitalization and antibiotic treatment; dose delays; OS and DFS; tumor response; toxicity
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation/allocation concealment (selection bias)	Low risk	Quote: "[…] patients were randomized […]" Comment: sequence generation was n.r. Allocation concealment was n.r. Patient characteristics at baseline were similarly distributed. Sample size > 100 patients
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "[...] a double-blind administration of lenograstim versus vehicle was chosen." Comment: n.s.* whether placebo was identically looking but owing to use of vehicle, adequate process of blinding was assumed; possible risk of unblinding owing to CSF-

Chevallier 1995 (*Continued*)

		specific adverse drug reactions
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: blinding of outcome assessment n.r.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "[...] 16 withdrew from the study (13 placebo and three lenograstim) for the following reasons [...]" Comment: attrition rate 13%; reasons for withdrawal were n.r. separately for each group; attrition rate was not equally distributed between groups
Selective reporting (reporting bias)	Low risk	Comment: no indication for selective reporting
Definitions and measurements of outcomes	Low risk	Comment: FN clearly defined; body temperature was measured twice daily, blood cell counts daily
Supportive treatment	Unclear risk	Comment: systemic antibiotic treatment in case of FN; precisely described clinical procedural method; patients in CGs were assumed to have received antibiotics more frequent

Del Giglio 2008

Methods	Design: 3-arm, open-label Phase III trial Follow-up: 10 months Ethical approval: yes
Participants	No. of patients randomized: 348 No. of patients evaluated: 348 Stage of cancer: high-risk breast cancer stage II-IV Demographics: women, age range 25 to 74 years Setting: multicenter study; Belarus, Slovenia, South Africa, Brazil, Chile, Russia, Hungary, Lithuania, Romania, Poland Informed consent: yes (written)
Interventions	CSF intervention: G-CSF: filgrastim (XM02 or Neupogen), 5 μg/kg/d; d2 until ANC $\geq 10 \times 10^9$/L after nadir (minimum until d6, maximum until d15) sc Control: identical placebo Basic treatment: doxorubicin 60 mg/m^2, DCT 75 mg/m^2; d1 i.v.; every 21d; maximum 4 cycles Supportive treatment: no information about administration of antibiotics

Outcomes	Primary outcome measures: duration of neutropenia in cycle 1 Secondary outcome measures: incidence of FN; ANC profile
Notes	Drug approval study for a filgrastim biosimilar (XM02)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation/allocation concealment (selection bias)	Unclear risk	Quote: "[...] patients were randomized in a 2:2:1 ratio [...]" Comment: sequence generation was n.r.; allocation concealment was n.r. Slight differences in the distribution of prior radiation therapy between treatment arms: IG1 (XM02): 10.7%, IG2(Neupogen): 6.6%; CG: 12.5%. Sample size > 100 patients
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "A true double-blind design was not feasible because XM02 and Neupogen were formulated in different volumes. [...]" Comment: unblinded study personnel; blinding of patients was unclear; no details about the placebo were reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "investigator was kept blinded and performed all assessments [...]" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Nine patients (2.6%) discontinued the study due to an AE [adverse event], i.e., 2(1.4%) patients in the XM02 group [...]" Comment: attrition rate 2.6%; reasons for withdrawal were n.r. separately for each group
Selective reporting (reporting bias)	Low risk	Antibiotic treatment was n.r.
Definitions and measurements of outcomes	Unclear risk	2 different definitions of FN; it was not stated which was applied Daily measurement of body temperature and blood cell counts
Supportive treatment	Unclear risk	Quote: "Secondary endpoints included [...] and of protocol defined FN (administration of systemic antibiotics) [...]"

		Comment: patients in CGs were assumed to have received antibiotics more frequently

Hansen 1995

Methods	Design: 2-arm, open-label, Phase III trial Follow-up: unclear Ethical approval: yes
Participants	No. of patients randomized: 20 No. of patients evaluated: 18 (for tumor response) Stage of cancer: metastatic breast cancer, stage IV Demographics: women, age range 37-61 years (median age: CSF IG: 56 years; CG: 50 years) Setting: single-center study; Denmark Informed consent: yes (n.s.)
Interventions	CSF intervention: GM-CSF: molgramostim, 5 µg/kg/d; d2-11 sc Control: no treatment Basic treatment: HD-cyclophosphamide 2.5 g/m^2; d1 i.v.; or HD-epirubicin 130 mg/m^2; d1 i.v.; every 21d; 4 cycles Supportive treatment: antibiotics (i.v.) for treatment of FN (if applied as primary or secondary prophylaxis was unclear)
Outcomes	Primary outcome measures: neutropenia duration Secondary outcome measures: FN duration; ANC profiles; antibiotic usage owing to FN; hospitalization; FN events; tumor response
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation/allocation concealment (selection bias)	High risk	Quote: "[...] patients were randomly assigned to [...]" Comment: sequence generation was n.r. Allocation concealment was n.r. Differences existed in pretreatment and in sites of metastases. Sample size < 100 patients
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: no statements about blinding or any use of placebo, thus we judged the study as an open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: unblinded outcome assessment

Hansen 1995 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "In the treatment arm two patient's did not receive all [...] courses [...] In the control arm, one patient ceased treatment [...]" Comment: attrition rate 15%; reasons stated for each group
Selective reporting (reporting bias)	Unclear risk	Reporting the incidence of events instead and no rates of patients with neutropenia
Definitions and measurements of outcomes	Unclear risk	FN not defined; daily measuring of body temperature and blood cell counts
Supportive treatment	Unclear risk	Comment: incidence and duration of antibiotic treatment was a secondary outcome measure, criteria of administration was not stated

Jones 1996

Methods	Design: 2 arm, double-blind, placebo-controlled, Phase III trial Follow-up: 5 years poststudy to monitor disease status and survival Ethical approval: yes
Participants	No. of patients randomized: 142 No. of patients evaluated: 131 Stage of cancer: T1N1 - T2N1- others (stage II-III) Demographics: women, age range 25 to 69 years (mean age 47 years) Setting: single-center study; USA Informed consent: yes
Interventions	CSF intervention: GM-CSF: sargramostim, 250 µg/m^2; d3-15 sc Control: identical placebo Basic treatment: FAC-MD: fluorouracil 600 mg/m^2, cyclophosphamide 750 mg/m^2, antimycin 60 mg/m^2; d1 i.v.; every 21d; 4 cycles Supportive treatment: prophylactic antibiotics (i.v., oral, or both) at the onset of grade III neutropenia (ANC < 1000/µL)
Outcomes	Primary outcome measures: neutropenia duration Secondary outcome measures: neutropenia incidence; FN incidence; dose intensity; hospitalization; antibiotic use owing to FN; toxicity
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Jones 1996 (*Continued*)

Random sequence generation/allocation concealment (selection bias)	Low risk	Quote: "[...] patients were randomized to [...]" Comment: sequence generation was n. r. Allocation concealment was n.r. There were no significant differences in sociodemographic and disease related parameters. Sample size > 100 patients
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Patients [...] received the study drug [...] in a double blind manner"; "[...] equivalent volume of placebo [...]" Comment: method of blinding adequate; unblinding owing to specific adverse drug reactions could not be ruled out
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: blinding of outcome assessment n.r.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "there were three early withdrawals among patients randomized to placebo and eight among patients randomized to GM-CSF" Comment: attrition rate 8%; reasons stated for each study group; attrition rate was not equally distributed between groups
Selective reporting (reporting bias)	Low risk	Comment: no indication for selective reporting
Definitions and measurements of outcomes	Low risk	FN clearly defined; body temperature was measured daily and blood cell counts 3 times weekly
Supportive treatment	Unclear risk	Quote: "[…] at the onset of grade 3 neutropenia (ANC<1000/µl) patients received prophylactic antibiotics" Comment: patients in CGs were assumed to have received antibiotics more frequently

Muhonen 1996

Methods	Design: 2-arm, open label, Phase III trial Follow-up: unclear Ethical approval: unclear

Muhonen 1996 (*Continued*)

Participants	No. of patients randomized: 32 No. of patients evaluated: 31 Stage of cancer: metastatic or loco-regionally advanced breast cancer Demographics: women, age range 34 to 65 years (median age: IG: 51 years; CG: 52 years) Setting: multicenter study; Finland Informed consent: yes (verbal)
Interventions	CSF intervention: G-CSF: filgrastim, 5 µg/kg; d4-17 sc Control: no treatment Basic treatment: MMM-StD: mitomycin 8 mg/m^2 d1, mitoxantrone 8 mg/m^2 d1 and 22, methotrexate 35 mg/m^2 d1 and 22; i.v.; every 42d; 6 cycles Supportive treatment: no information about the administration of antibiotics
Outcomes	Primary outcome measure: neutropenia incidence Secondary outcome measures: infections; toxicity; dose delays; tumor response; survival
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation/allocation concealment (selection bias)	Unclear risk	Quote: "Patients [...] were randomly assigned to [...]" Comment: sequence generation was n.r. Allocation concealment was n.r. Slight differences in hormone pretreatment. Sample size < 100 patients
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: no statements about blinding or any use of placebo, thus we judged the study as an open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: unblinded outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "one patient did not fulfil the entry criteria [...] and was removed from the study [...]" Comment: attrition rate 1%; no drop-outs during study period
Selective reporting (reporting bias)	High risk	Comment: no information on rates or events of FN provided

Muhonen 1996 (*Continued*)

Definitions and measurements of outcomes	High risk	FN not defined; no statements about body temperature measurements and blood cell counts
Supportive treatment	Unclear risk	Comment: no information about administration of antibiotics

Papaldo 2003

Methods	Design: 4-arm, open-label, Phase III trial Follow-up: median 55 months Ethical approval: yes
Participants	No. of patients randomized: 506 No. of patients evaluated: 497 Stage of cancer: stage I or II breast cancer Demographics: women, age range 25 to 65 years (median age: IG1: 47 years; IG2: 48 years; CG1: 47 years; CG2: 47 years) Setting: multicenter study; Italy Informed consent: yes
Interventions	CSF intervention: G-CSF: filgrastim, 5 different schedules: 480 µg/d, d8 - 14; 480 µg/d, d8,10,12,14; 300 µg/, d8 - 14; 300 µg/d, d8,10,12,14; 300 µg/d, d8, 12; Control: no treatment Basic treatment: epirubicin 120 mg/m^2, cyclophosphamide 600 mg/m^2; d1 i.v.; every 21d; 4 cycles Supportive treatment: antibiotics (i.v.) for treatment of a documented infection
Outcomes	Primary outcome measures: DFS and OS Secondary outcome measures: FN incidence; neutropenia incidence; toxicity
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation/allocation concealment (selection bias)	Unclear risk	Quote: "[...] were randomly assigned to [...] patients and tumor characteristics were well balanced among the groups" Comment: sequence generation was n.r. Allocation concealment was n.r. Slight differences in numbers of patients with involved lymph nodes, tumor size and receptor status between study arms. Sample size > 100 patients

Papaldo 2003 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: no statements about blinding or any use of placebo; thus we judged the study as an open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: unblinded outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Nine patients were not assessable for DFS and OS because [...]" Comment: attrition rate 2%; reasons for withdrawal were n.r. separately for each group
Selective reporting (reporting bias)	Unclear risk	Number of documented infections n.r.
Definitions and measurements of outcomes	High risk	FN clearly defined; no information about measurements of body temperature, blood cell counts once weekly
Supportive treatment	Unclear risk	Quote: "[...] antibiotics given for a documented infection"

Romieu 2007

Methods	Design: 2 arm, open-label, Phase II trial Follow-up: 16 months Ethical approval: yes
Participants	No. of patients randomized: 60 No. of patients evaluated: 59 Stage of cancer: node-positive breast cancer stage II-III Demographics: women, age range 65 to 77 years Setting: multicenter study; Germany, Spain, Italy, France Informed consent: yes (written)
Interventions	CSF intervention: G-CSF: pegfilgrastim, 6 mg/d; d2 sc Control: no treatment in cycle 1 Basic treatment: FEC-100: 5-fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, cyclophosphamide 500 mg/m^2; d1 i.v.; every 21d; 4 to 6 cycles Supportive treatment: secondary prophylaxis with antibiotics in case of FN
Outcomes	Primary outcome measure: neutropenic events in cycle 1 Secondary outcome measures: neutropenic events (all cycles); dose intensity; ANC profiles
Notes	-

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation/allocation concealment (selection bias)	Unclear risk	Quote: "[...] based on an open-label predetermined randomization schedule generated by a statistician [...] treatment groups were randomly assigned (1:1) using an interactive voice response system" Comment: owing to the reported procedure, we assumed an adequate sequence generation and concealed allocation. Sample size < 100 patients
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "this open-label, phase 2 study [...]" Comment: unblinded patients and personnel
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: unblinded outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "three patients in the PP [primary prophylaxis] group and four from the SP [secondary prophylaxis] group were withdrawn [...]" Comment: attrition rate 12%; reasons stated for each study group
Selective reporting (reporting bias)	Unclear risk	Comment: no outcome on hematologic data (ANC, etc.) provided; antibiotic treatment was n.r
Definitions and measurements of outcomes	Low risk	FN clearly defined; daily measuring of body temperature; blood cell counts were taken 3 times weekly
Supportive treatment	Unclear risk	Quote: "secondary prophylaxis (antibiotic) was allowed in patients who developed FN" Comment: patients in CGs seemed to have received antibiotics more frequently

Vogel 2005

Methods	Design: 2-arm, double blind, placebo-controlled, Phase III trial Follow-up: not stated Ethical approval: yes
Participants	No. of patients randomized: 928 No. of patients evaluated: 928 Stage of cancer: metastatic and non-metastatic breast cancer Demographics: women (922), men (6), age range 21 to 88 years (mean 52 years) Setting: multicenter study; 88 sites in Europe and the USA Informed consent: yes
Interventions	CSF intervention: G-CSF: pegfilgrastim, 6 mg; d2 sc; Control: identical placebo Basic treatment: DCT-HD: DCT 100 mg/m^2; d1 i.v.; every 21d; 4 cycles Supportive treatment: antibiotics (i.v.) secondary prophylaxis for FN treatment; non-narcotic analgesics and opioids for bone pain
Outcomes	Primary outcome measure: FN incidence Secondary outcome measures: neutropenia incidence; hospitalization; antibiotic usage owing to FN; dose delays; toxicity
Notes	Large multinational drug approval study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation/allocation concealment (selection bias)	Unclear risk	Quote: "Patients were randomly assigned to [...] the groups were well matched in characteristics [...]" Comment: sequence generation was n.r.; allocation concealment was n.r. Slight differences in percentages of previous radiation therapy and chemotherapy and in first quartile of ANC. Sample size > 100 patients
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "[...] all patients received at least one dose of blinded study drug [...] and placebo were presented as identical prefilled syringes" Comment: identical placebo; unblinding owing to specific adverse drug reactions could not be ruled out
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: blinding of outcome assessment n.r.

Vogel 2005 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "thirty-five patients (8%) in the initial placebo group and 27 (6%) in the pegfilgrastim group withdrew from the study" Comment: attrition rate 7%; reasons stated for each study group
Selective reporting (reporting bias)	Unclear risk	Comment: number of dropped-out patients in cycle 1 not stated
Definitions and measurements of outcomes	Unclear risk	FN not clearly defined; body temperature was measured twice daily, blood cell counts once weekly in case of fever
Supportive treatment	Unclear risk	Quote: "[...] the incidence of need for IV anti-infectives as a result of FN." Comment: patients in CGs were assumed to have received antibiotics more frequently

ANC: absolute neutrophil count; CG: control group; CSF: colony-stimulating factors; d: day; DCT: docetaxel; DFS: disease-free survival; FAC: fluorouracil, antimycin, cyclophosphamide; FEC: fluorouracil, epirubicin, cyclophosphamide; FEC-HD: fluorouracil, epirubicin, cyclophosphamide high-dose; FN: febrile neutropenia; G-CSF: granulocyte colony-stimulating factors; GM-CSF: granulocyte-macrophage colony-stimulating factors; HD: high-dose; IG: intervention group; ITT: intention-to-treat; i.v.: intravenous; MMM: mitomycin, mitoxantrone, methotrexate; No.: number; n.r.: not reported; n.s.: not significant; OS: overall survival; sc: subcutaneous.

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

Study	Reason for exclusion
Ardizzoni 1994	Different chemotherapy schedules between study arms
Athanassiou 1996	Different chemotherapy schedules between study arms
Bono 2009	Different basic treatments between study arms; no placebo or no-treatment control
Ellis 2011	Different basic treatments between study arms
Gascon 2010	No placebo or no-treatment control
Gebbia 1994	No data available for breast cancer patients; author was contacted several times but did not answer
Green 2003	No placebo or no-treatment control

(*Continued*)

Hatam 2011	Different basic treatments between study arms and no application of CSFs
Holmes 2002	No placebo or no-treatment control
Holmes 2002b	No placebo or no-treatment control
Iiristo 2011	Different basic treatments between study arms
Ikonomidis 2008	Study reported only biochemical parameters and no outcomes of interest of our systematic review. Study author was contacted for additional data but did not answer
Joensuu 2010	Different basic treatments between study arms
Khrichkova 2008	No information about randomization and recruitment of patients. Study did not report on outcomes of interest for our systematic review
Martin 2006	Different basic treatments between study arms
Schröder 1999	No placebo or no-treatment control
Steger 1992	Not clear how many patients were included in the trial. The publication reports only data for injection-site reaction experienced by patients receiving GM-CSF. Author was contacted but could not provide data
Stöger 1998	Different chemotherapy schedules between study arms
Tomova 2009	Different basic treatments between study arms
Venturini 2005	Patients in the G-CSF arm received chemotherapy every 2 weeks, while patients in the control arms received chemotherapy every 3 weeks
von Minckwitz 2008a	Treatment with CSFs was not randomly allocated
von Minckwitz 2010	Different basic treatments between study arms
von Minckwitz 2011	Different basic treatments between study arms and no control arm with placebo or no treatment
Waller 2010	No placebo or no-treatment control
Wang 2004	Unclear cross-over design; no placebo or no-treatment control
Weaver 2001	No placebo or no-treatment control
Yau 1996	Outcomes of interests of our review only reported aggregated with data from patients with lymphoma. Author was contacted but did not answer
Zhang 1999	Cross-over study; no placebo or no-treatment control

(*Continued*)

Zhou 2006	No placebo or no-treatment control

CSF: colony-stimulating factors; G-CSF: granulocyte colony-stimulating factors; GM-CSF: granulocyte-macrophage colony-stimulating factors.

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

Amgen 2015

Trial name or title	A Prospective Observational Study of Neutropenia and Anemia Management in Subjects With Solid Tumors Receiving Myelotoxic Chemotherapy
Methods	Prospective observational study
Participants	Breast cancer, non-small cell lung cancer, ovarian cancer and small cell lung cancer patients; the aim is to have approximately 800 breast cancer, 300 non-small cell lung cancer, 100 small-cell lung cancer and 100 ovarian cancer subjects
Interventions	Chemotherapy and primary, secondary or no usage of G-CSF
Outcomes	Primary outcome measure: incidence of febrile neutropenia; secondary outcome measure: G-CSF use, ESA use, anti-infective use, transfusions and hospitalizations
Starting date	December 2007
Contact information	Amgen Call Center
Notes	-

ESA: erythropoiesis-stimulating agents; G-CSF: granulocyte colony-stimulating factor.

DATA AND ANALYSES

Comparison 1. Primary outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Febrile neutropenia rates (total)	6	2073	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.11, 0.70]
1.1 G-CSF	5	1931	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.10, 0.75]
1.2 GM-CSF	1	142	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.03, 2.24]
2 Febrile neutropenia rates (all cycles)	2	598	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.09, 2.24]
2.1 G-CSF	2	598	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.09, 2.24]
3 Febrile neutropenia rates (first cycles)	4	1475	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.08, 0.52]
3.1 G-CSF	3	1333	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.06, 0.61]
3.2 GM-CSF	1	142	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.03, 2.24]
4 Early mortality	8	2143	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.13, 0.77]
4.1 G-CSF	6	1981	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.13, 0.77]
4.2 GM-CSF	2	162	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Infection-related mortality	8	2143	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.02, 1.29]
5.1 G-CSF	6	1981	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.02, 1.29]
5.2 GM-CSF	2	162	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 2. Secondary Outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Neutropenia grade IV (total)	4	712	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.17, 1.18]
1.1 G-CSF	3	570	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.05, 2.44]
1.2 GM-CSF	1	142	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.62, 0.97]
2 Neutropenia grade IV (all cycle)	2	511	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.08, 0.45]
2.1 G-CSF	2	511	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.08, 0.45]
2.2 GM-CSF	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Neutropenia grade IV (first cycle)	2	201	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.66, 1.21]
3.1 G-CSF	1	59	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.79, 1.43]
3.2 GM-CSF	1	142	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.62, 0.97]
4 Infections (total)	3	210	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.72, 1.02]
4.1 G-CSF	3	210	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.72, 1.02]
5 Hospitalization (total)	4	1149	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.06, 0.30]
5.1 G-CSF	2	987	Risk Ratio (M-H, Fixed, 95% CI)	0.12 [0.05, 0.29]
5.2 GM-CSF	2	162	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.04, 1.56]
6 Hospitalization (all cycles)	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.01, 6.10]
6.1 GM-CSF	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.01, 6.10]
7 Hospitalization (first cycle)	3	1129	Risk Ratio (M-H, Fixed, 95% CI)	0.13 [0.06, 0.30]

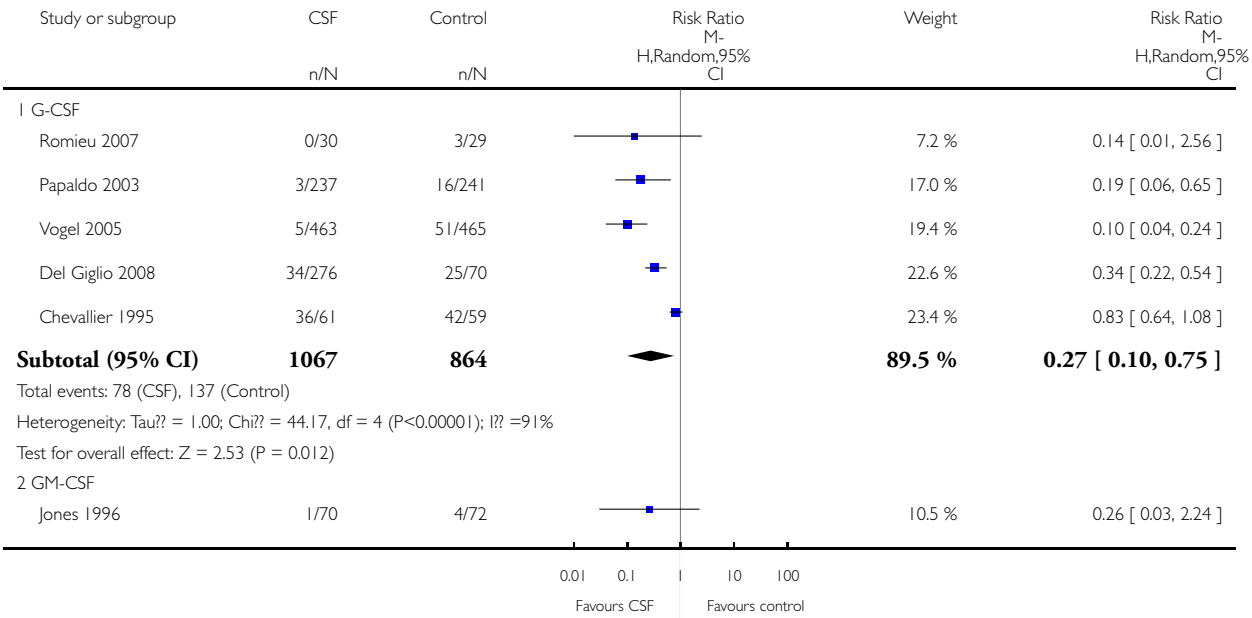
7.1 G-CSF	2	987	Risk Ratio (M-H, Fixed, 95% CI)	0.12 [0.05, 0.29]
7.2 GM-CSF	1	142	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.03, 2.24]
8 Antibiotics (total)	4	1568	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.22, 0.55]
8.1 G-CSF	2	1406	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.22, 0.57]
8.2 GM-CSF	2	162	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.04, 1.56]
9 Antibiotics (all cycles)	2	498	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.28, 0.87]
9.1 G-CSF	1	478	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.29, 0.90]
9.2 GM-CSF	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.01, 6.10]
10 Antibiotics (first cycle)	2	1070	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.03, 4.77]
10.1 G-CSF	1	928	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.07, 0.46]
10.2 GM-CSF	1	142	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.76, 0.95]
11 Chemotherapy, planned dose in time	4	1588	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.97, 1.13]
11.1 G-CSF	4	1588	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.97, 1.13]
12 Bone pain	2	151	Risk Ratio (M-H, Fixed, 95% CI)	5.88 [2.54, 13.60]
12.1 G-CSF	2	151	Risk Ratio (M-H, Fixed, 95% CI)	5.88 [2.54, 13.60]
13 Injection-site reaction	2	262	Risk Ratio (M-H, Fixed, 95% CI)	3.59 [2.33, 5.53]
13.1 G-CSF	1	120	Risk Ratio (M-H, Fixed, 95% CI)	3.39 [1.85, 6.20]
13.2 GM-CSF	1	142	Risk Ratio (M-H, Fixed, 95% CI)	3.81 [2.05, 7.05]

Analysis 1.1. Comparison 1 Primary outcomes, Outcome 1 Febrile neutropenia rates (total).

Review: Primary prophylactic colony-stimulating factors for the prevention of chemotherapy-induced febrile neutropenia in breast cancer patients

Comparison: 1 Primary outcomes

Outcome: 1 Febrile neutropenia rates (total)



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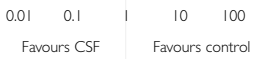
Study or subgroup	CSF n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**70**	**72**		**10.5 %**	**0.26 [0.03, 2.24]**
Total events: 1 (CSF), 4 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.23 (P = 0.22)					
Total (95% CI)	**1137**	**936**		**100.0 %**	**0.27 [0.11, 0.70]**
Total events: 79 (CSF), 141 (Control)					
Heterogeneity: Tau?? = 0.96; Chi?? = 44.82, df = 5 (P<0.00001); I?? =89%					
Test for overall effect: Z = 2.72 (P = 0.0065)					
Test for subgroup differences: Chi?? = 0.00, df = 1 (P = 0.96), I?? =0.0%					



Analysis 1.2. Comparison 1 Primary outcomes, Outcome 2 Febrile neutropenia rates (all cycles).

Review: Primary prophylactic colony-stimulating factors for the prevention of chemotherapy-induced febrile neutropenia in breast cancer patients

Comparison: 1 Primary outcomes

Outcome: 2 Febrile neutropenia rates (all cycles)

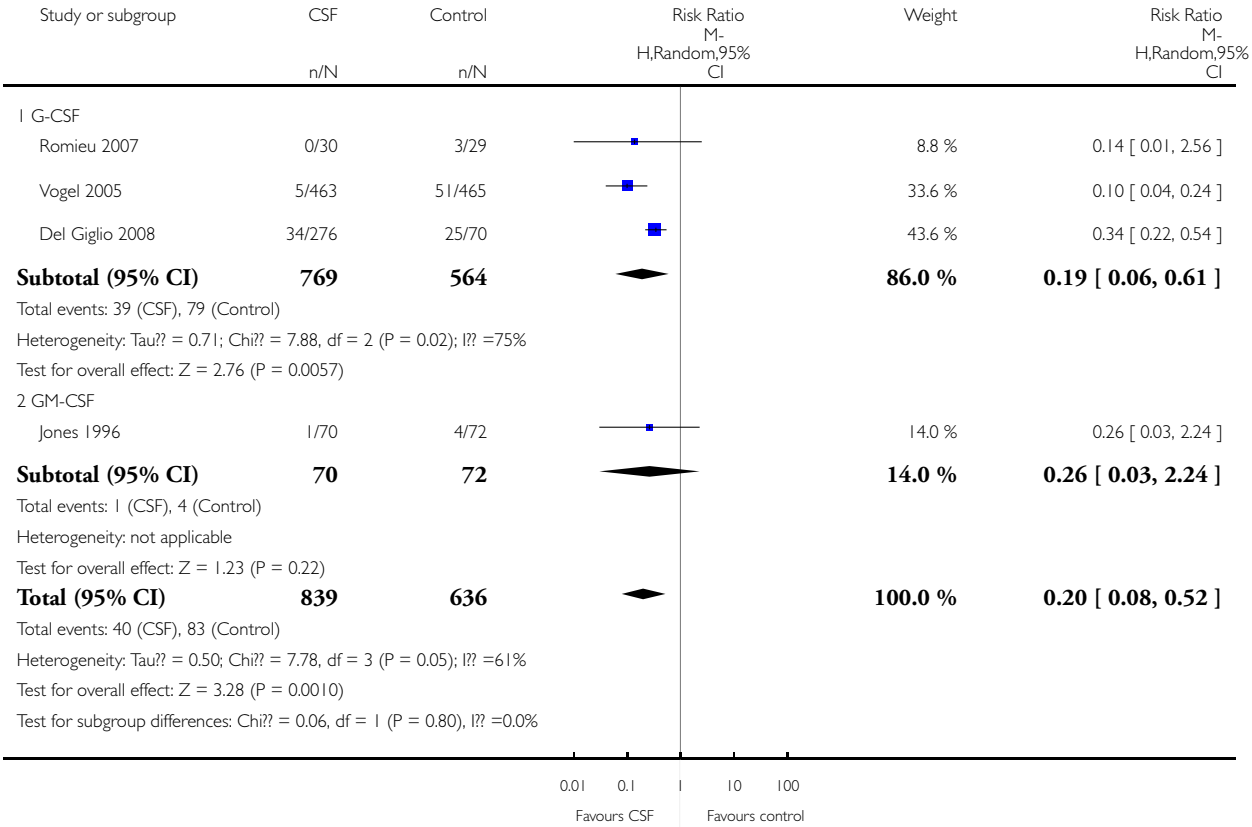
Study or subgroup	CSF n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 G-CSF					
Papaldo 2003	3/237	16/241		43.4 %	0.19 [0.06, 0.65]
Chevallier 1995	36/61	42/59		56.6 %	0.83 [0.64, 1.08]
Total (95% CI)	**298**	**300**		**100.0 %**	**0.44 [0.09, 2.24]**
Total events: 39 (CSF), 58 (Control)					
Heterogeneity: Tau?? = 1.21; Chi?? = 6.94, df = 1 (P = 0.01); I?? =86%					
Test for overall effect: Z = 0.99 (P = 0.32)					
Test for subgroup differences: Not applicable					

Analysis 1.3. Comparison 1 Primary outcomes, Outcome 3 Febrile neutropenia rates (first cycles).

Review: Primary prophylactic colony-stimulating factors for the prevention of chemotherapy-induced febrile neutropenia in breast cancer patients

Comparison: 1 Primary outcomes

Outcome: 3 Febrile neutropenia rates (first cycles)



Analysis 1.4. Comparison 1 Primary outcomes, Outcome 4 Early mortality.

Review: Primary prophylactic colony-stimulating factors for the prevention of chemotherapy-induced febrile neutropenia in breast cancer patients

Comparison: 1 Primary outcomes

Outcome: 4 Early mortality

Study or subgroup	CSF n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 G-CSF				
Chevallier 1995	0/61	0/59		0.0 [0.0, 0.0]
Papaldo 2003	0/254	0/243		0.0 [0.0, 0.0]
Muhonen 1996	0/16	0/15		0.0 [0.0, 0.0]
Romieu 2007	0/30	1/29		0.32 [0.01, 7.61]
Del Giglio 2008	1/276	2/70		0.13 [0.01, 1.38]
Vogel 2005	5/463	14/465		0.36 [0.13, 0.99]
Subtotal (95% CI)	**1100**	**881**		**0.32 [0.13, 0.77]**
Total events: 6 (CSF), 17 (Control)				
Heterogeneity: Chi?? = 0.62, df = 2 (P = 0.73); I?? =0.0%				
Test for overall effect: Z = 2.55 (P = 0.011)				
2 GM-CSF				
Jones 1996	0/70	0/72		0.0 [0.0, 0.0]
Hansen 1995	0/11	0/9		0.0 [0.0, 0.0]
Subtotal (95% CI)	**81**	**81**		**0.0 [0.0, 0.0]**
Total events: 0 (CSF), 0 (Control)				
Heterogeneity: Chi?? = 0.0, df = 0 (P<0.00001); I?? =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Total (95% CI)	**1181**	**962**		**0.32 [0.13, 0.77]**
Total events: 6 (CSF), 17 (Control)				
Heterogeneity: Chi?? = 0.62, df = 2 (P = 0.73); I?? =0.0%				
Test for overall effect: Z = 2.55 (P = 0.011)				
Test for subgroup differences: Not applicable				

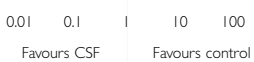
Analysis 1.5. Comparison 1 Primary outcomes, Outcome 5 Infection-related mortality.

Review: Primary prophylactic colony-stimulating factors for the prevention of chemotherapy-induced febrile neutropenia in breast cancer patients

Comparison: 1 Primary outcomes

Outcome: 5 Infection-related mortality

Study or subgroup	CSF n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 G-CSF				
Chevallier 1995	0/61	0/59		0.0 [0.0, 0.0]
Muhonen 1996	0/16	0/15		0.0 [0.0, 0.0]
Papaldo 2003	0/254	0/243		0.0 [0.0, 0.0]
Romieu 2007	0/30	0/29		0.0 [0.0, 0.0]
Del Giglio 2008	0/276	1/70		0.09 [0.00, 2.08]
Vogel 2005	0/463	2/465		0.20 [0.01, 4.17]
Subtotal (95% CI)	**1100**	**881**		**0.14 [0.02, 1.29]**
Total events: 0 (CSF), 3 (Control)				
Heterogeneity: Chi?? = 0.15, df = 1 (P = 0.70); I?? =0.0%				
Test for overall effect: Z = 1.73 (P = 0.083)				
2 GM-CSF				
Hansen 1995	0/11	0/9		0.0 [0.0, 0.0]
Jones 1996	0/70	0/72		0.0 [0.0, 0.0]
Subtotal (95% CI)	**81**	**81**		**0.0 [0.0, 0.0]**
Total events: 0 (CSF), 0 (Control)				
Heterogeneity: Chi?? = 0.0, df = 0 (P<0.00001); I?? =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Total (95% CI)	**1181**	**962**		**0.14 [0.02, 1.29]**
Total events: 0 (CSF), 3 (Control)				
Heterogeneity: Chi?? = 0.15, df = 1 (P = 0.70); I?? =0.0%				
Test for overall effect: Z = 1.73 (P = 0.083)				
Test for subgroup differences: Not applicable				

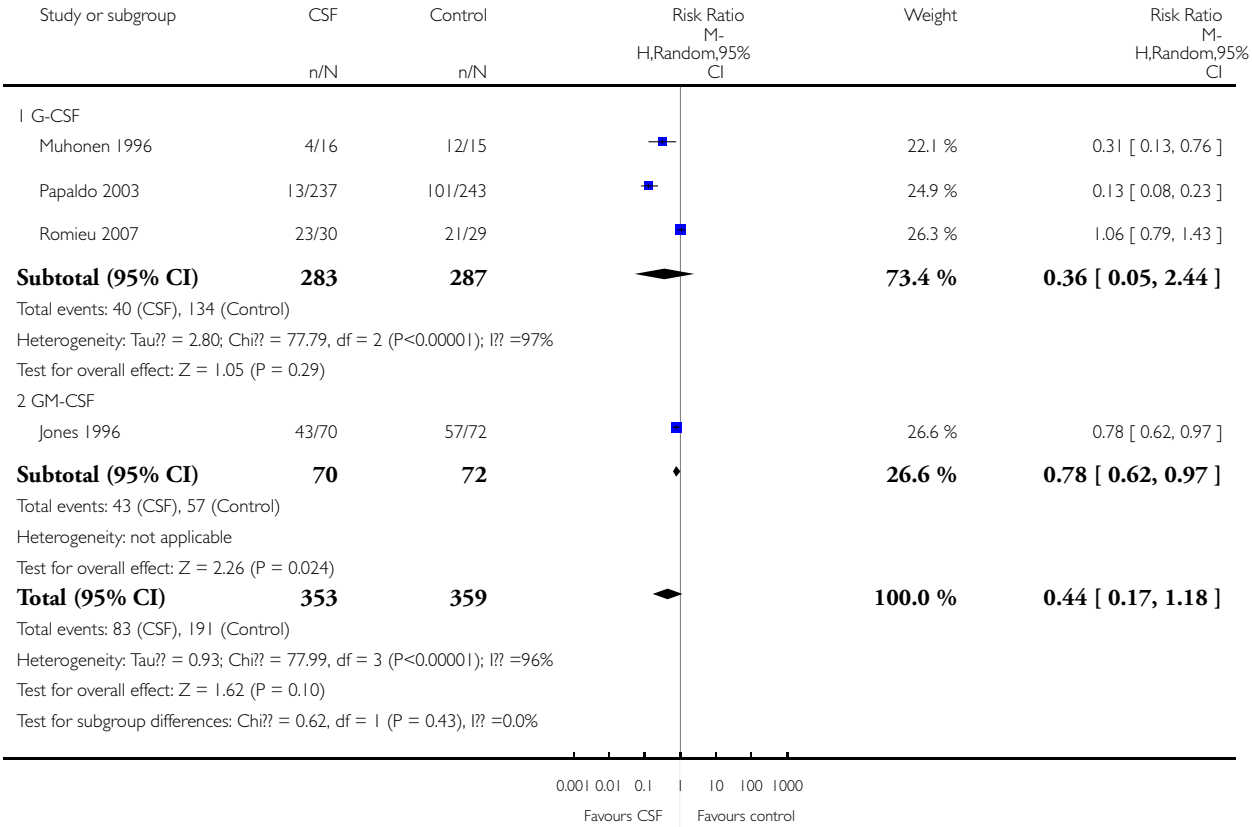


Analysis 2.1. Comparison 2 Secondary Outcomes, Outcome 1 Neutropenia grade IV (total).

Review: Primary prophylactic colony-stimulating factors for the prevention of chemotherapy-induced febrile neutropenia in breast cancer patients

Comparison: 2 Secondary Outcomes

Outcome: 1 Neutropenia grade IV (total)



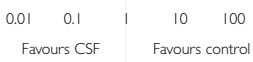
Analysis 2.2. Comparison 2 Secondary Outcomes, Outcome 2 Neutropenia grade IV (all cycle).

Review: Primary prophylactic colony-stimulating factors for the prevention of chemotherapy-induced febrile neutropenia in breast cancer patients

Comparison: 2 Secondary Outcomes

Outcome: 2 Neutropenia grade IV (all cycle)

Study or subgroup	CSF n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 G-CSF					
Muhonen 1996	4/16	12/15		42.1 %	0.31 [0.13, 0.76]
Papaldo 2003	13/237	101/243		57.9 %	0.13 [0.08, 0.23]
Subtotal (95% CI)	**253**	**258**		**100.0 %**	**0.19 [0.08, 0.45]**
Total events: 17 (CSF), 113 (Control)					
Heterogeneity: Tau?? = 0.25; Chi?? = 2.80, df = 1 (P = 0.09); I?? =64%					
Test for overall effect: Z = 3.79 (P = 0.00015)					
2 GM-CSF					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (CSF), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**253**	**258**		**100.0 %**	**0.19 [0.08, 0.45]**
Total events: 17 (CSF), 113 (Control)					
Heterogeneity: Tau?? = 0.25; Chi?? = 2.80, df = 1 (P = 0.09); I?? =64%					
Test for overall effect: Z = 3.79 (P = 0.00015)					
Test for subgroup differences: Not applicable					

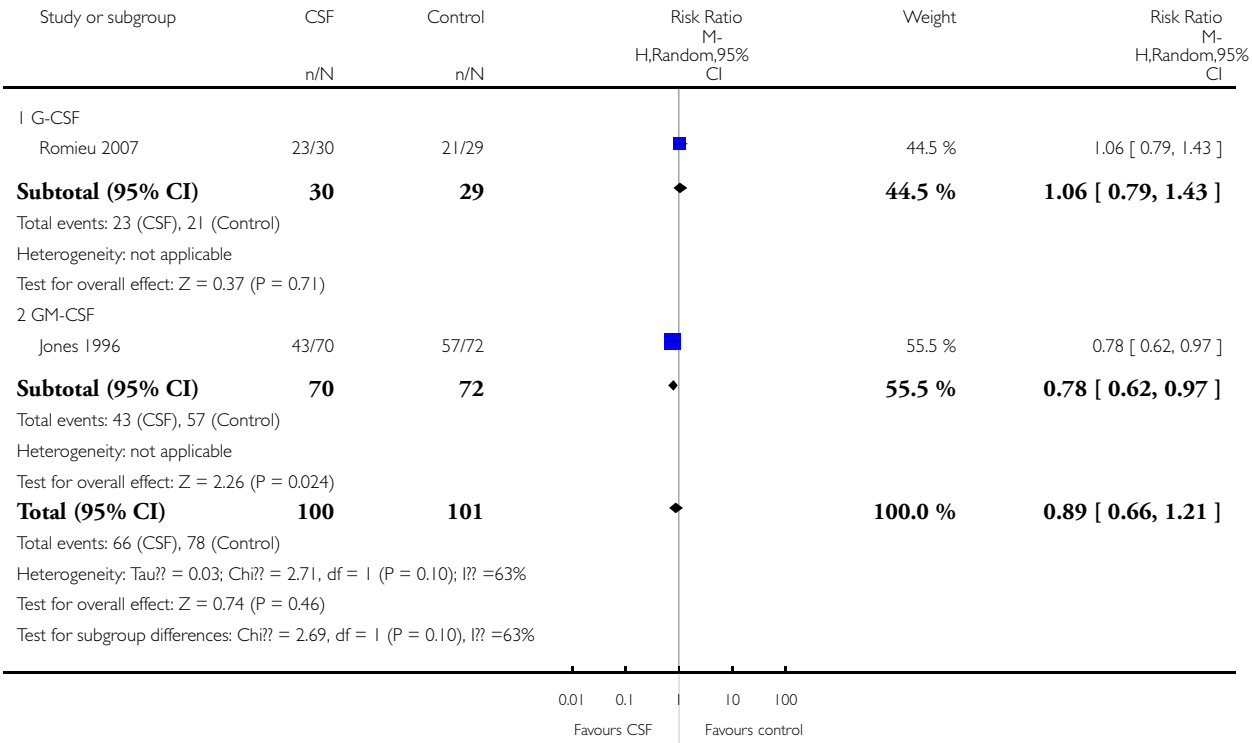


Analysis 2.3. Comparison 2 Secondary Outcomes, Outcome 3 Neutropenia grade IV (first cycle).

Review: Primary prophylactic colony-stimulating factors for the prevention of chemotherapy-induced febrile neutropenia in breast cancer patients

Comparison: 2 Secondary Outcomes

Outcome: 3 Neutropenia grade IV (first cycle)

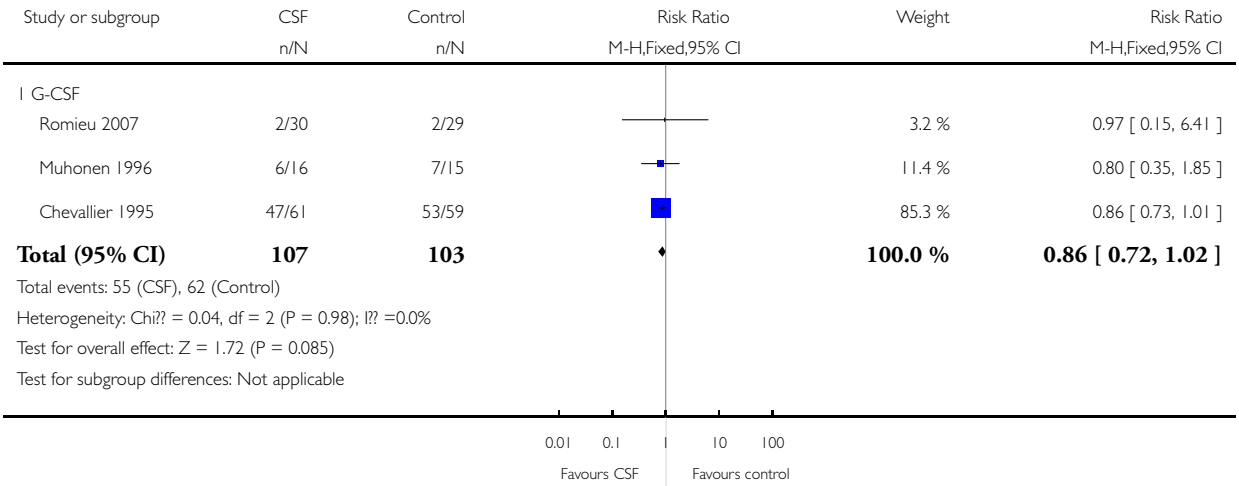


Analysis 2.4. Comparison 2 Secondary Outcomes, Outcome 4 Infections (total).

Review: Primary prophylactic colony-stimulating factors for the prevention of chemotherapy-induced febrile neutropenia in breast cancer patients

Comparison: 2 Secondary Outcomes

Outcome: 4 Infections (total)

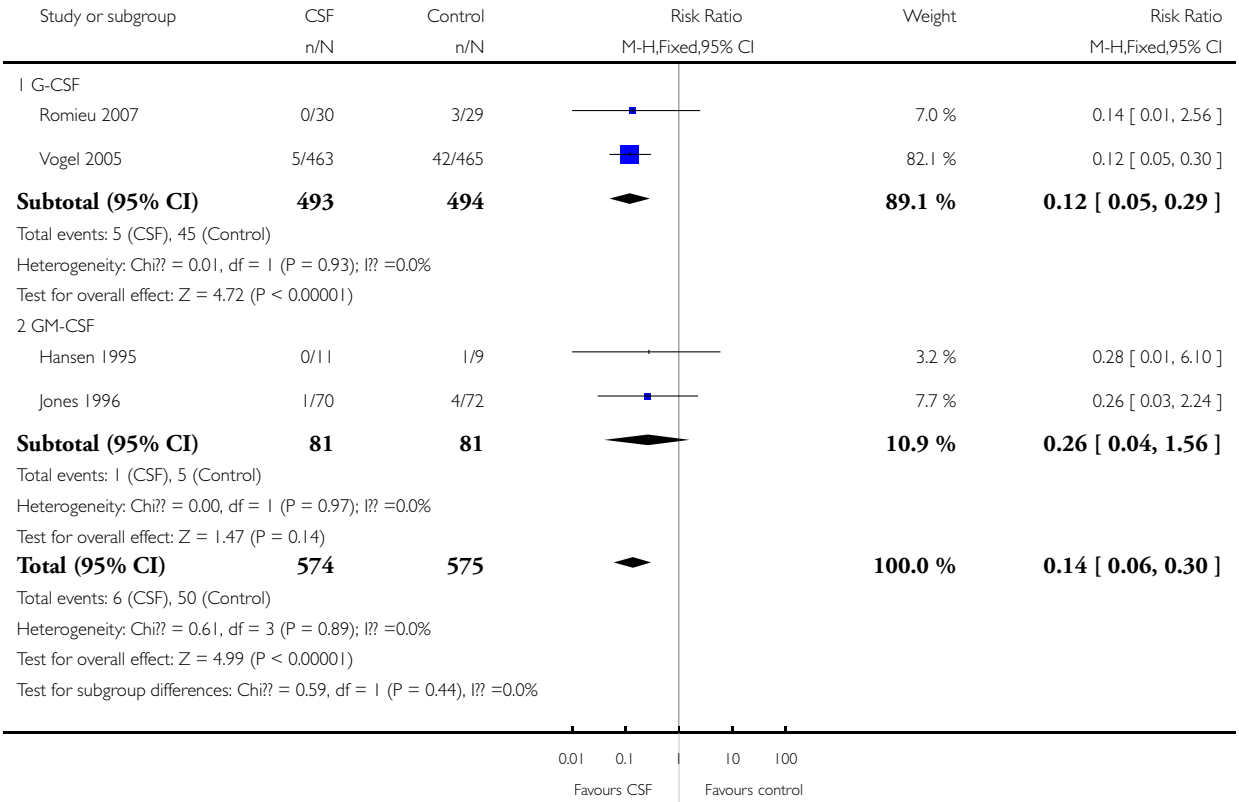


Analysis 2.5. Comparison 2 Secondary Outcomes, Outcome 5 Hospitalization (total).

Review: Primary prophylactic colony-stimulating factors for the prevention of chemotherapy-induced febrile neutropenia in breast cancer patients

Comparison: 2 Secondary Outcomes

Outcome: 5 Hospitalization (total)

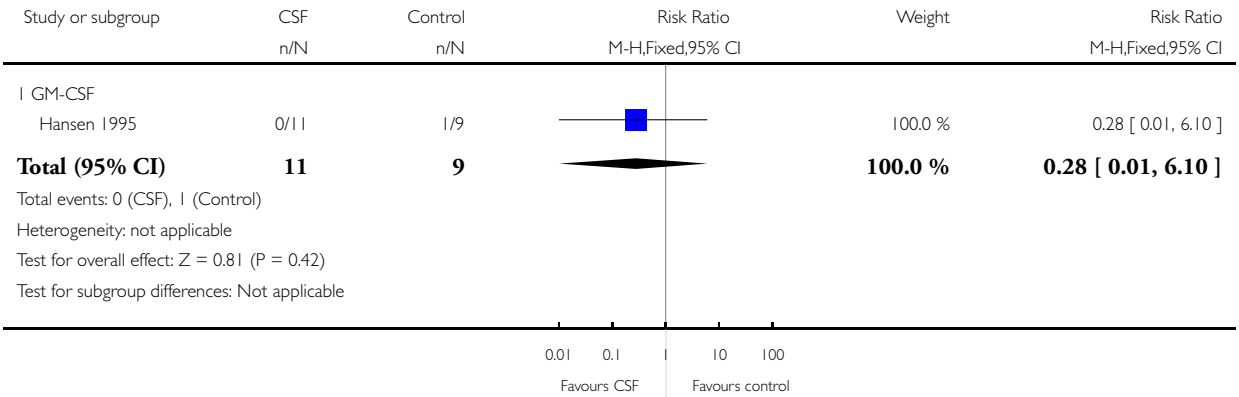


Analysis 2.6. Comparison 2 Secondary Outcomes, Outcome 6 Hospitalization (all cycles).

Review: Primary prophylactic colony-stimulating factors for the prevention of chemotherapy-induced febrile neutropenia in breast cancer patients

Comparison: 2 Secondary Outcomes

Outcome: 6 Hospitalization (all cycles)



Analysis 2.7. Comparison 2 Secondary Outcomes, Outcome 7 Hospitalization (first cycle).

Review: Primary prophylactic colony-stimulating factors for the prevention of chemotherapy-induced febrile neutropenia in breast cancer patients

Comparison: 2 Secondary Outcomes

Outcome: 7 Hospitalization (first cycle)

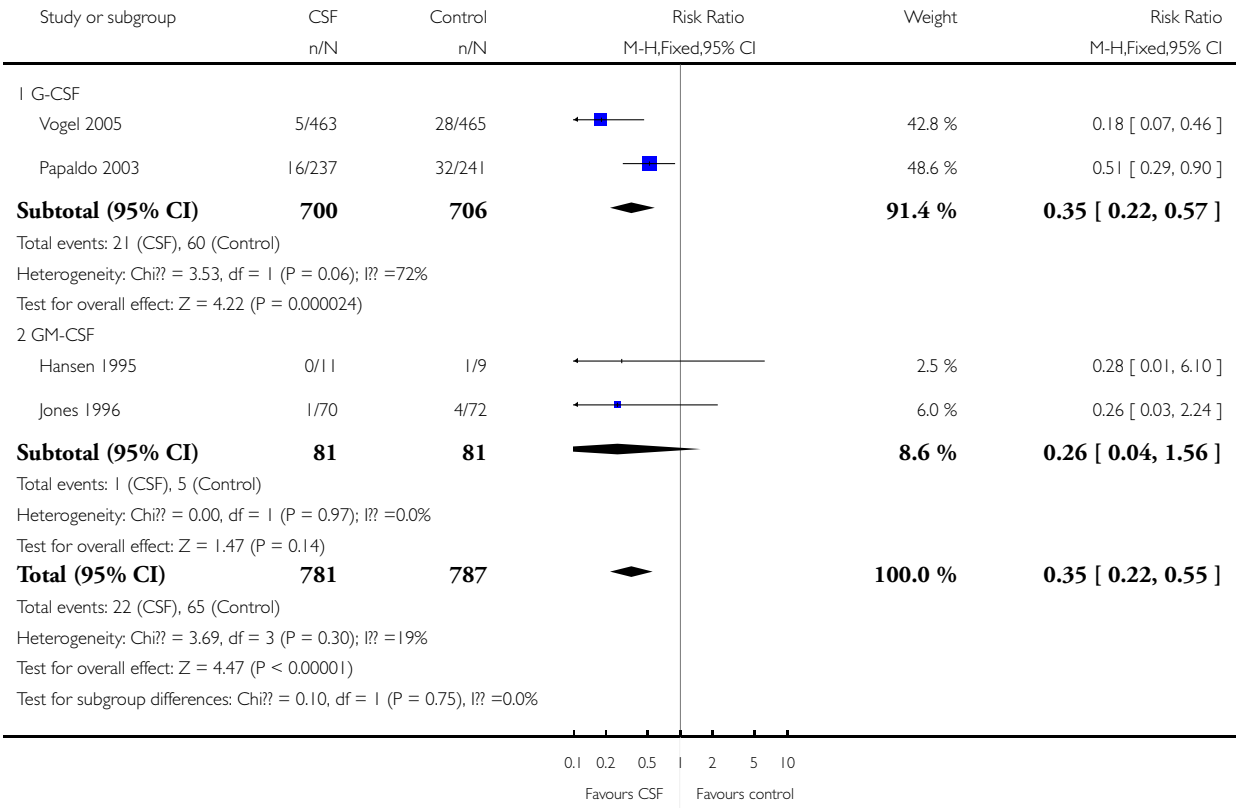
Study or subgroup	CSF n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 G-CSF					
Romieu 2007	0/30	3/29		7.2 %	0.14 [0.01, 2.56]
Vogel 2005	5/463	42/465		84.8 %	0.12 [0.05, 0.30]
Subtotal (95% CI)	**493**	**494**		**92.0 %**	**0.12 [0.05, 0.29]**
Total events: 5 (CSF), 45 (Control)					
Heterogeneity: Chi?? = 0.01, df = 1 (P = 0.93); I?? =0.0%					
Test for overall effect: Z = 4.72 (P < 0.00001)					
2 GM-CSF					
Jones 1996	1/70	4/72		8.0 %	0.26 [0.03, 2.24]
Subtotal (95% CI)	**70**	**72**		**8.0 %**	**0.26 [0.03, 2.24]**
Total events: 1 (CSF), 4 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.23 (P = 0.22)					
Total (95% CI)	**563**	**566**		**100.0 %**	**0.13 [0.06, 0.30]**
Total events: 6 (CSF), 49 (Control)					
Heterogeneity: Chi?? = 0.41, df = 2 (P = 0.81); I?? =0.0%					
Test for overall effect: Z = 4.91 (P < 0.00001)					
Test for subgroup differences: Chi?? = 0.40, df = 1 (P = 0.53), I?? =0.0%					

Analysis 2.8. Comparison 2 Secondary Outcomes, Outcome 8 Antibiotics (total).

Review: Primary prophylactic colony-stimulating factors for the prevention of chemotherapy-induced febrile neutropenia in breast cancer patients

Comparison: 2 Secondary Outcomes

Outcome: 8 Antibiotics (total)

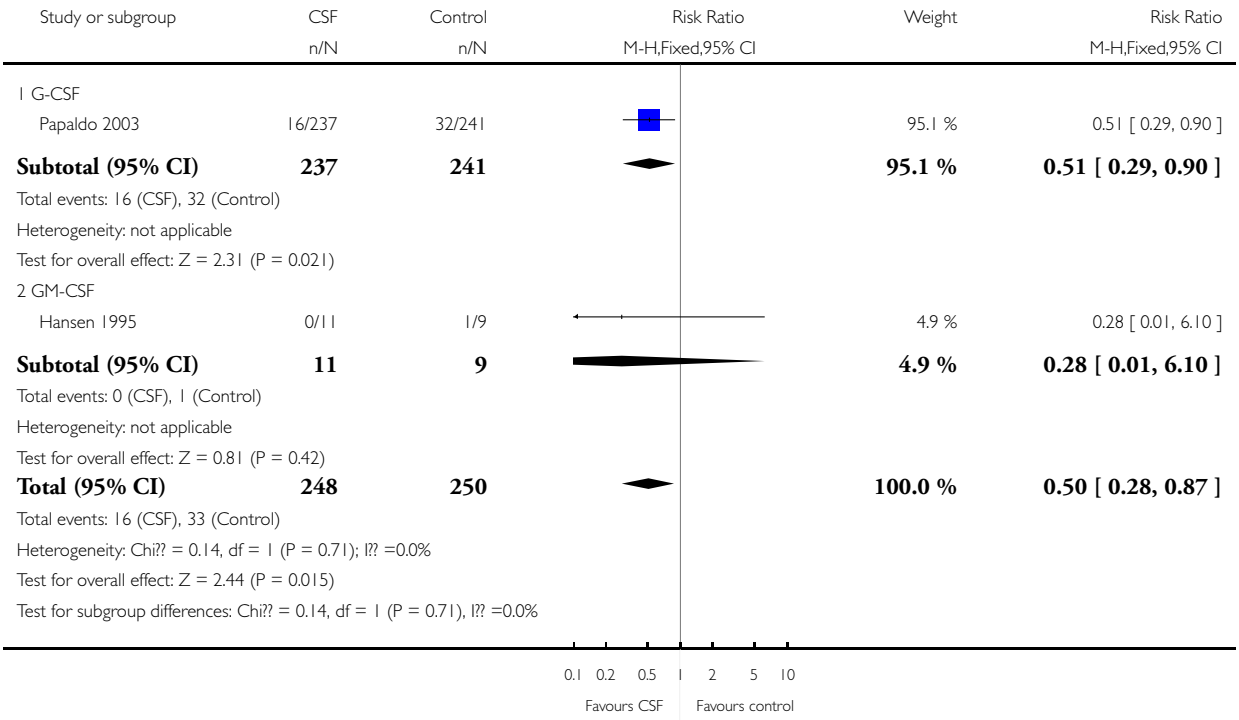


Analysis 2.9. Comparison 2 Secondary Outcomes, Outcome 9 Antibiotics (all cycles).

Review: Primary prophylactic colony-stimulating factors for the prevention of chemotherapy-induced febrile neutropenia in breast cancer patients

Comparison: 2 Secondary Outcomes

Outcome: 9 Antibiotics (all cycles)

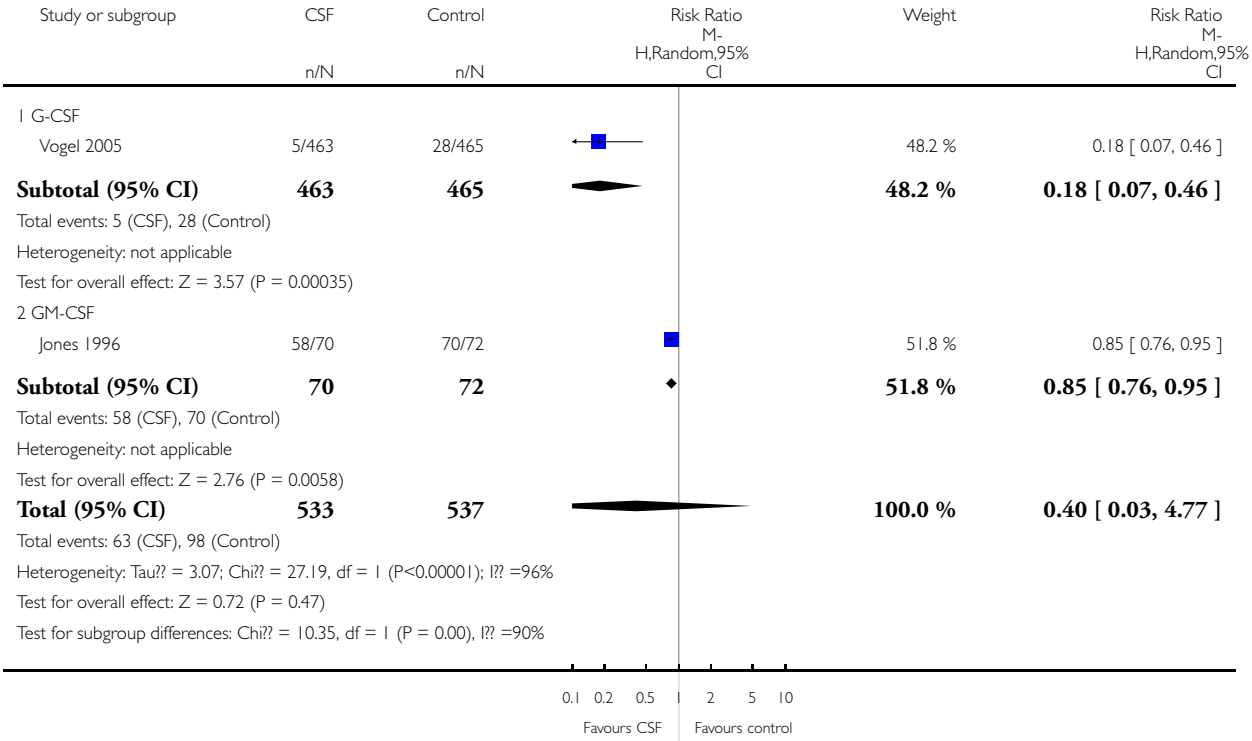


Analysis 2.10. Comparison 2 Secondary Outcomes, Outcome 10 Antibiotics (first cycle).

Review: Primary prophylactic colony-stimulating factors for the prevention of chemotherapy-induced febrile neutropenia in breast cancer patients

Comparison: 2 Secondary Outcomes

Outcome: 10 Antibiotics (first cycle)



Analysis 2.11. Comparison 2 Secondary Outcomes, Outcome 11 Chemotherapy, planned dose in time.

Review: Primary prophylactic colony-stimulating factors for the prevention of chemotherapy-induced febrile neutropenia in breast cancer patients

Comparison: 2 Secondary Outcomes

Outcome: 11 Chemotherapy, planned dose in time

Study or subgroup	CSF n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 G-CSF					
Romieu 2007	17/30	7/29		1.1 %	2.35 [1.15, 4.81]
Chevallier 1995	49/58	34/46		11.4 %	1.14 [0.93, 1.40]
Vogel 2005	370/463	363/465		38.4 %	1.02 [0.96, 1.09]
Papaldo 2003	238/243	243/254		49.0 %	1.02 [0.99, 1.06]
Total (95% CI)	**794**	**794**		**100.0 %**	**1.05 [0.97, 1.13]**
Total events: 674 (CSF), 647 (Control)					
Heterogeneity: Tau?? = 0.00; Chi?? = 7.65, df = 3 (P = 0.05); I?? =61%					
Test for overall effect: Z = 1.15 (P = 0.25)					
Test for subgroup differences: Not applicable					

Analysis 2.12. Comparison 2 Secondary Outcomes, Outcome 12 Bone pain.

Review: Primary prophylactic colony-stimulating factors for the prevention of chemotherapy-induced febrile neutropenia in breast cancer patients

Comparison: 2 Secondary Outcomes

Outcome: 12 Bone pain

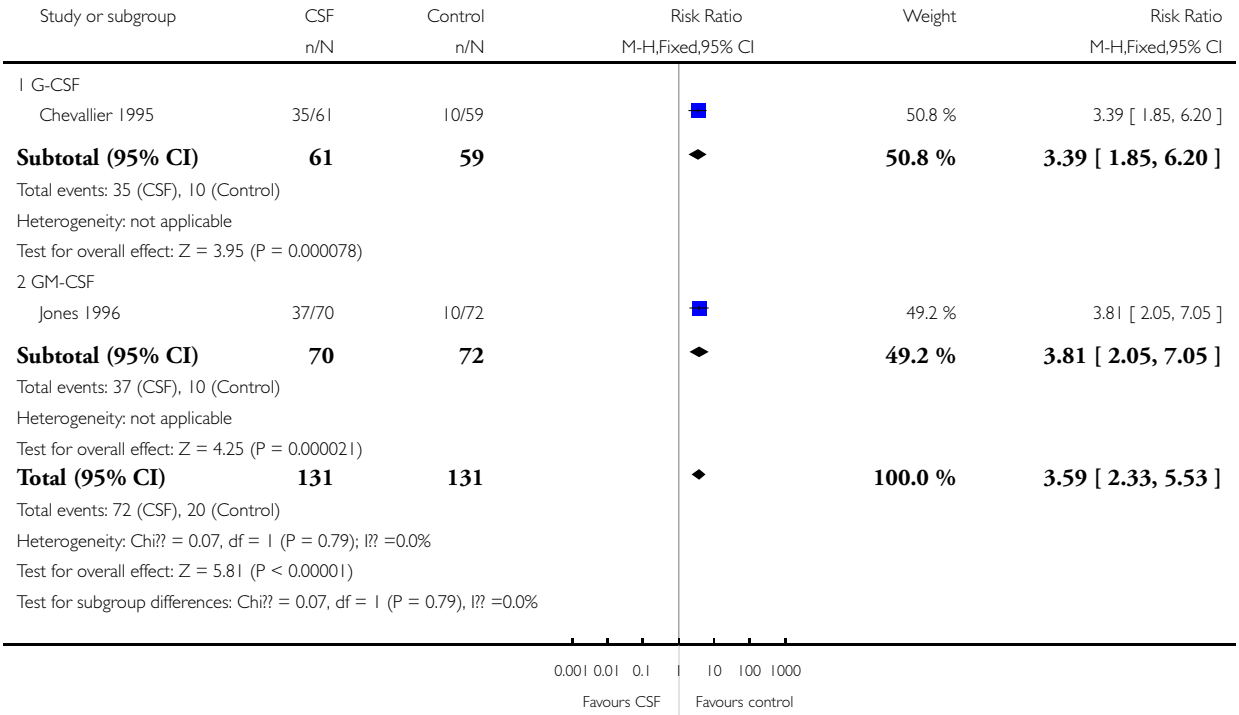
Study or subgroup	CSF n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 G-CSF					
Muhonen 1996	3/16	0/15		9.2 %	6.59 [0.37, 117.77]
Chevallier 1995	30/61	5/59		90.8 %	5.80 [2.42, 13.94]
Total (95% CI)	**77**	**74**		**100.0 %**	**5.88 [2.54, 13.60]**
Total events: 33 (CSF), 5 (Control)					
Heterogeneity: Chi?? = 0.01, df = 1 (P = 0.93); I?? =0.0%					
Test for overall effect: Z = 4.13 (P = 0.000036)					
Test for subgroup differences: Not applicable					

Analysis 2.13. Comparison 2 Secondary Outcomes, Outcome 13 Injection-site reaction.

Review: Primary prophylactic colony-stimulating factors for the prevention of chemotherapy-induced febrile neutropenia in breast cancer patients

Comparison: 2 Secondary Outcomes

Outcome: 13 Injection-site reaction



ADDITIONAL TABLES

Table 1. Characteristics of studies - chemotherapy regimen

Study	Chemotherapy
Chevallier 1995	Agents (FEC-HD): 5-fluorouracil: 750 mg/m^2, d1-4; epirubicin: 35 mg/m^2 d2-4; cyclophosphamide: 400 mg/m^2, d2-4 Schedule: every 3 weeks Cycles: 4
Jones 1996	Agents (FAC): 5-fluorouracil: 600 mg/m^2, d1; doxorubicin 60 mg/m^2 d1; cyclophosphamide: 750 mg/m^2, d1 Schedule: every 3 weeks Cycles: 4

Table 1. Characteristics of studies - chemotherapy regimen (*Continued*)

Del Giglio 2008	Agents: (TA) doxorubicin: 60 mg/m^2, d1, docetaxel: 75 mg/m^2, d1 Schedule: every 3 weeks Cycles: 4
Romieu 2006	Agents (FEC): 5-fluorouracil: 500 mg/m^2, d1; epirubicin: 100 mg/m^2, d1; cyclophosphamide: 500 mg/m^2, d1 Schedule: every 3 weeks Cycles: 4-6 cycles
Papaldo 2003	Agents (EC): epirubicin: 120 mg/m^2, d1; cyclophosphamide: 600 mg/m^2, d1 Schedule: every 3 weeks Cycles: 4
Hansen 1995	Agents (HD-E/HD-C): cyclophosphamide: 2.5 g/m^2, d1 or epirubicin: 130 mg/m^2, d1 Schedule: every 3 weeks Cycles: 4
Vogel 2005	Agents (D): docetaxel: 100 mg/m^2, d1 Schedule: every 3 weeks Cycles: 4
Muhonen 1996	Agents (MMM): mitomycin: 8 mg/m^2, d1; mitoxantrone: 8 mg/m^2, d1 and 22; methotrexate: 35 mg/m^2 d1 and 22 Schedule: every 6 weeks Cycles: 6

d: day.

Table 2. Characteristics of studies - type of applied CSF

Study	CSF	Type	Dosage and administration
Chevallier 1995	G-CSF	Lenograstim (filgrastim) rHuG-CSF	5 µg/kg/d (d6-15)
Del Giglio 2008		XM02/Neupogen (filgrastim) r-metHuG-CSF	5 µg/kg/d (d2-6/15)
Muhonen 1996		Filgrastim	5 µg/kg/d (d4-17/d24-37)
Papaldo 2003		Filgrastim	cohort 1: 480 µg/d (d8-14) cohort 2: 480 µg/d (d8, 10, 12, 14) cohort 3: 300 µg/d (d8-14) cohort 4: 300 µg/d (d8, 10, 12, 14) cohort 5: 300 µg/d (d8, 12)
Vogel 2005		Neulasta (pegfilgrastim) rHuG-CSF	6 mg (d2)

Table 2. Characteristics of studies - type of applied CSF (*Continued*)

Romieu 2006		Pegfilgrastim	6 mg (d2)
Hansen 1995	GM-CSF	Molgramostim	5 µg/kg/d (d2-11)
Jones 1996		Sargramostim	250 µg/m^2 (d3-15)

CSF: colony-stimulating factors; d: day of administration; G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; rHuG-CSF: recombinant human colony-stimulating factor

Table 3. Results - definition and measurement of febrile neutropenia

Study	Definition		Measurement	
	Fever (°C)	Neutropenia (WHO grade)	Fever • time point • time period • measured by • documented in	Neutropenia
Chevallier 1995	≥ 38.2	III and IV	• twice daily • during CX and after discharge • recorded by a nurse • diary	daily (1st cycle) 3 times/week (2nd to 4th cycle)
Jones 1996	≥ 38.2	IV	• each morning • while on study • patients (ucl) • diary	thrice/week
Del Giglio 2008	2 different definitions, unclear which was applied		• daily • from d1 until at least d15 • n.r. • n.r.	from d2 until at least d15
Romieu 2006	> 38.0	IV	• daily • during CX until d30 after study • n.r. • n.r.	3 times/week until ANC ≥ 2.0 × 10^9/L then weekly
Papaldo 2003	≥ 38.2	IV	• n.r. • n.r. • n.r. • n.r.	weekly
Hansen 1995	n.r.	n.r.	• daily • between each cycle	daily

Table 3. Results - definition and measurement of febrile neutropenia (*Continued*)

			• n.r. • n.r.	
Vogel 2005	≥ 38.2	IV (on the same day of fever or day after)	• twice daily • n.r. • patient • n.r.	weekly if febrile
Muhonen 1996	n.r.	n.r.	• n.r. • n.r. • n.r. • n.r.	n.r.

ANC: absolute neutrophil count; CX: chemotherapy; d: day of administration; n.r.: not reported.

Table 4. Results - rates of neutropenia/febrile neutropenia

Study	CSF	Neutropenia grade IV		Neutropenia grade III-IV		Febrile neutropenia	
		Intervention	Control	Intervention	Control	Intervention	Control
Chevallier 1995	G-CSF	-	-	-	-	36/61 (59%) E/Cy: 47/240 (19.6%)	42/59 (71.2%) ns E/Cy: 67/214 (31.3%)
Del Giglio 2008 (1st cycle)		-	-	-	-	34/276 12.3%	25/70 (36.1%)*
Muhonen 1996		4/16 (25%)	12/15 (80%)*	-	-	-	-
Papaldo 2003		13/237 (5.4%)	101/243 (41.6%)	68/237 (28.6%)	198/243 (81.6%)*	3/237 (1.2%)	16/241 (6.6%)*
Vogel 2005		-	-	-	-	6/463 (1%) 1st cycle: 5/463 < 1%	78/465 (17%) * 1st cycle: 51/465 11%
Romieu 2006 (1st cycle)		23/30 (77%)	21/29 (72%)	-	-	1/30 (3.3%)	5/29 (17.2%)‡

Table 4. Results - rates of neutropenia/febrile neutropenia (*Continued*)

Hansen 1995	GM-CSF	E/Cy: 24/39 (62%)	E/Cy: 29/31 (94%)	-	-	E/Cy: 8/39 (21%)	E/Cy: 10/31 (32%)
Jones 1996 (1st cycle)		43/70 (61%)	57/72 (79%)	-	-	6/70 (9%) 1st cycle: 1/70 (1%)	8/72 (11%) 1st cycle: 4/72 (6%)

* = significant (P < 0.05).

‡ + stated as serious febrile neutropenia events.

CSF: colony-stimulating factor; E/Cy: events per cycle; G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; ns: not significant.

Table 5. Results - early mortality

Study	CSF	Reason	Number of events	
			Intervention	Control
Chevallier 1995	G-CSF	-	0/61	0/59
Del Giglio 2008		IG: ischemic stroke; CG: sepsis, cardiorespiratory arrest	1/276 (0.3%)	2/70 (2.9%)
Vogel 2005		IG: 5; CG: 12, all attributed to disease progression; CG: 2, related to infectious events	5/463 (1%)	14/465* (3%)
Romieu 2006		CG: cardiac failure	0/30	1/29
Hansen 1995		-	0/11	0/9
Papaldo 2003		-	0/254	0/243
Jones 1996	GM-CSF	-	0/70	0/72
Muhonen 1996		-	0/16	0/15

* - significant (P < 0.05).

CG: control group; CSF: colony-stimulating factor; G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; IG: intervention group.

Table 6. Results - infection related mortality

Study	CSF	Reason	Number of events	
			Intervention	Control
Chevallier 1995	G-CSF	-	0/61	0/59
Del Giglio 2008		during cycle 1: CG: 1 sepsis	0/276	1/70 (1.4%)
Vogel 2005		CG: 2 sepsis	0/463	2/465 (0.4%)
Romieu 2006		-	0/30	0/29
Hansen 1995		-	0/11	0/9
Papaldo 2003		-	0/254	0/243
Jones 1996	GM-CSF	-	0/70	0/72
Muhonen 1996		-	0/16	0/15

CG: control group; CSF: colony-stimulating factor; G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor.

Table 7. Results - duration of severe neutropenia (grade IV)

Study	CSF	Duration of neutropenia grade IV (days)	
		Intervention	Control
Chevallier 1995	G-CSF	2	6*
Romieu 2006		1st cycle: 1 (mn)	1st cycle: 3 (mn)
Del Giglio 2008		1st cycle: 1.1 (mn)	1st cycle: 3.9 (mn)
Hansen 1995	GM-CSF	4 (md)	8 (md)
Jones 1996		1st cycle: 2 (md)	1st cycle: 7* (md)

* = significant (P < 0.05).

CSF: colony-stimulating factor; G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; md: median; mn: mean.

Table 8. Results - rates of patients with infections

Study	CSF	Intervention	Control
Chevallier 1995	G-CSF	47/61 (77%)	53/59 (89.8%) ns
Muhonen 1996		6/16 (37.5%)	7/15 (46.7%) ns
Romieu 2006 (1st cycle)	GM-CSF	2/30 (7%)	2/29 (7%) ns

CSF: colony-stimulating factor; G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; ns: not significant.

Table 9. Results - hospitalization and administration of antibiotics

Study	CSF	Hospitalization			Administration of antibiotics			
		Intervention	Control	Decision	Mode	Intervention	Control	Decision
Papaldo 2003	G-CSF	-	-	-	i.v.	16/237 (7%)	32/241* (13%)	Not stated
Vogel 2005		6/463 (1%) 1st cycle: 5/463 (1%)	64/465 (14%)* 1st cycle: 42/465 (9%) nsp	In case of a clinical diagnosis of FN	i.v.	7/463 (2%) 1st cycle: 1%	48/465 (10%)* 1st cycle: 6%	In case of FN
Romieu 2006		0/30 (0%)	3/29 (10,3%)	In case of FN (N4 and > 38 °C)	i.v.	-	-	-
Hansen 1995	GM-CSF	0/11 (0%)	1/9 (11%) nsp	Not stated	i.v.	0/11 (0%)	1/9 (11%) nsp	Not stated
Jones 1996		6/70 (9%) 1st cycle: 1/70 (1%)	8/72 (11%) 1st cycle: 4/72 nsp (6%)	In case of FN	Ciprofloxacin orally twice daily (500 mg) i.v.	1st cycle: 58/70 (83%) 1/70 (1%)	1st cycle: 70/72 (97%) 4/72 (6%)	At the onset of N3 until recovery patients received antibiotics (orally) Hospitalized patients received an-

Table 9. Results - hospitalization and administration of antibiotics (*Continued*)

								tibiotics (i.v.)

* = significant (P < 0.05).

CSF: colony-stimulating factor; FN: febrile neutropenia; G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; i.v.: intravenous; N3: grade III neutropenia; N4: grade IV neutropenia; nsp: not specified.

Table 10. Results - administration of chemotherapies

Study	CSF	Rates of patients who received the planned chemotherapy cycles at scheduled times and doses	
		Intervention	Control
Chevallier 1995	G-CSF	Retreatment at the planned date for cycles 2, 3, 4 51/61 (84%) 51/60 (85%) 49/58 (84%)	46/57 (81%) 33/52 (63%) 34/46 (74%)
Papaldo 2003		Epirubicin dose intensity: 98.1%	95.5%
Vogel 2005		Patients who received planned dose on time: 80%	78%
Romieu 2006		RDI 100%: 17 (57%) RDI 95% to 100%: 9 (30%) RDI 90% to 95%: 2 (7%) RDI < 90%: 2 (7%)	7 (24%) 12 (41%) 6 (21%) 4 (14%)

CSF: colony-stimulating factor; G-CSF: granulocyte colony-stimulating factor; RDI: relative dose intensity.

Table 11. Results - adverse events

Study	CSF	Bone pain		Injection-site reactions	
		Intervention	Control	Intervention	Control
Chevallier 1995	G-CSF	30/61 (49%)	5/59 (8%)	35/61 (57%)	10/59 (17%)
Muhonen 1996		3/16 (19%)	0/15 (0%)	-	-
Papaldo 2003		101/237 (42.6%)	Not stated	-	-
Vogel 2005		146/463 (31%)	126/465 (27%)	-	-

Table 11. Results - adverse events (*Continued*)

Jones 1996	GM-CSF	-	-	37/70 (53%)	10/72 (14%)*

* = significant (P < 0.05).
CSF: colony-stimulating factor; G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor.

APPENDICES

Appendix 1. DIMDI search strategy

(colony-stimulating factors OR
granulocyte colony-stimulating factor OR
granulocyte colony stimulating factor, recombinant OR
granulocyte-macrophage colony-stimulating factor OR
granulocyte macrophage colony-stimulating factors, recombinant OR
filgrastim OR
granulocyte colony-stimulating factor OR
recombinant granulocyte colony stimulating factor OR
g csf OR
gcsf OR
granulocyte-macrophage colony-stimulating factor OR
gm csf OR
recombinant granulocyte macrophage colony-stimulating factor OR
gmcsf OR
pegfilgrastim OR
lenograstim OR
sargramostim OR
filgrastim OR
neupogen OR
granocyte OR
neulasta OR
biograstim OR
ratiograstim OR
XM02 OR
Immunex OR
Leukine OR
Leucomax OR
Molgramostin OR
Granulokin OR
Granulokine OR
Nivestim OR
Tevagrastim OR
Zarzio OR
SCH 39300 OR

Neupopeg OR
Regramostim OR
Prokine)
AND
(Control Group* OR
Placebos OR
Randomized Controlled Trial OR
Controlled Clinical Trial OR
Clinical Trial, Phase III OR
Clinical Trial, Phase IV OR
Placebos)
AND
(breast neoplasms OR
breast OR
carcinoma, ductal, breast OR
breast neoplasms OR
breast cancer OR
mamma OR
breast ductal carcinoma OR
mammary ductal carcinoma OR)
AND
(Antineoplastic protocols OR
Chemotherapy, adjuvant OR
Neoadjuvant therapy OR
Antineoplastic combined chemotherapy protocols OR
Chemotherapy)
limits: "Mensch" (human) AND "Krebserkrankungen" (cancer diseases)

Appendix 2. Clinicaltrials.gov and WHO ICTRP search strategy

WHO ICTRP "advanced search" strategy

in the title:
colony-stimulating factors OR
granulocyte colony-stimulating factor OR
granulocyte colony stimulating factor, recombinant OR
granulocyte-macrophage colony-stimulating factor OR
granulocyte macrophage colony-stimulating factors, recombinant OR
filgrastim OR
granulocyte colony-stimulating factor OR
recombinant granulocyte colony stimulating factor OR
g csf OR
gcsf OR
granulocyte-macrophage colony-stimulating factor OR
gm csf OR
recombinant granulocyte macrophage colony-stimulating factor OR
gmcsf OR
pegfilgrastim OR
lenograstim OR
sargramostim OR
filgrastim OR
neupogen OR

granocyte OR
neulasta OR
biograstim OR
ratiograstim OR
XM02 OR
Immunex OR
Leukine OR
Leucomax OR
Molgramostin OR
Granulokin OR
Granulokine OR
Nivestim OR
Tevagrastim OR
Zarzio OR
SCH 39300 OR
Neupopeg OR
Regramostim OR
Prokine
in the condition:
breast neoplasms OR
breast OR
carcinoma, ductal, breast OR
breast neoplasms OR
breast cancer OR
mamma OR
breast ductal carcinoma OR
mammary ductal carcinoma
in the intervention: -
all recruitment status
all countries
every date of registration

Clinicaltrials.gov search strategy

(colony-stimulating factors OR
granulocyte colony-stimulating factor OR
granulocyte colony stimulating factor, recombinant OR
granulocyte-macrophage colony-stimulating factor OR
granulocyte macrophage colony-stimulating factors, recombinant OR
filgrastim OR
granulocyte colony-stimulating factor OR
recombinant granulocyte colony stimulating factor OR
g csf OR
gcsf OR
granulocyte-macrophage colony-stimulating factor OR
gm csf OR
recombinant granulocyte macrophage colony-stimulating factor OR
gmcsf OR
pegfilgrastim OR
lenograstim OR
sargramostim OR
filgrastim OR
neupogen OR
granocyte OR
neulasta OR

biograstim OR
ratiograstim OR
XM02 OR
Immunex OR
Leukine OR
Leucomax OR
Molgramostin OR
Granulokin OR
Granulokine OR
Nivestim OR
Tevagrastim OR
Zarzio OR
SCH 39300 OR
Neupopeg OR
Regramostim OR
Prokine) [ALL-FIELDS]
AND "Interventional" [STUDY-TYPES]
AND
(breast neoplasms OR
breast OR
carcinoma AND ductal AND breast OR
breast neoplasms OR
breast cancer OR
mamma OR
breast ductal carcinoma OR
mammary ductal carcinoma) [DISEASE]

Appendix 3. Chinese Databases search strategy

VIP Database:

集落刺激因子**AND**发热性中性粒细胞减少(**ti**) **0**
集落刺激因子**AND**发热性中性粒细胞减少(**kw**) **0**
集落刺激因子 **AND FN** (**ti**) **0**
集落刺激因子 **AND FN** (**kw**) **4**
CSF AND 发热性中性粒细胞减少 (**ti**) **0**
CSF AND 发热性中性粒细胞减少 (**kw**) **0**
CSF AND FN (**ti**) **19**
CSF AND FN (**kw**) **15**

CNKI

集落刺激因子**AND**发热性中性粒细胞减少(**ti**) **0**
集落刺激因子**AND**发热性中性粒细胞减少(**kw**) **1**
集落刺激因子**AND**发热性中性粒细胞减少(**mesh**) **10**
集落刺激因子 **AND FN** (**ti**) **0**
集落刺激因子 **AND FN** (**kw**) **0**
集落刺激因子 **AND FN** (**mesh**) **14**
CSF AND 发热性中性粒细胞减少 (**ti**) **1**
CSF AND 发热性中性粒细胞减少 (**kw**) **0**
CSF AND 发热性中性粒细胞减少 (**mesh**) **10**
CSF AND FN (**ti**) **1**
CSF AND FN (**kw**) **0**
CSF AND FN (**mesh**) **61**

CBM Database
集落刺激因子**AND**发热性中性粒细胞减少(**ti**) **0**
集落刺激因子**AND**发热性中性粒细胞减少(**ab**) **3**
集落刺激因子 **AND FN** (**ti**) **0**
集落刺激因子 **AND FN** (**ab**) **5**
CSF AND 发热性中性粒细胞减少 (**ti**) **1**
CSF AND 发热性中性粒细胞减少 (**ab**) **4**
CSF AND FN (**ti**) **0**
CSF AND FN (**ab**) **17**

HISTORY

Protocol first published: Issue 3, 2009

Review first published: Issue 10, 2012

CONTRIBUTIONS OF AUTHORS

PR and MH had full access to all data in the review and take responsibility for the integrity of the data and the accuracy of the analysis.

Study concept and design: MH, SM, PR, MZ.

Inclusion and exclusion of studies: PR, SM, JL, JB, MH.

Acquisition of data: PR, SM.

Data entry and plausibility check: PR, SM, MH.

Analysis and interpretation of data: MH, PR, SM, JB, MZ.

Drafting of the manuscript: PR, MH with contributions from all other review authors.

Statistical analysis: MZ, PR, MH.

Study supervision: MH.

The review was part of the doctoral thesis of PR.

DECLARATIONS OF INTEREST

The authors certify that they have no affiliations with any organization or entity with a direct financial interest in the subject matter of the review. All steps of the review process were completely independent from any work previously undertaken on this subject.

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- No sources of support supplied

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The published protocol included 'mortality related to infections' as a primary outcome. We have since split up mortality to include: early mortality (during the study) and infection-related mortality (during the study) for clarity in the review.