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REVIEW ARTICLE

Colony-Stimulating Factors for Chemotherapy-Induced Febrile Neutropenia: A Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Purpose

Current treatment for febrile neutropenia (FN) includes hospitalization for evaluation, empiric broad-spectrum antibiotics, and other supportive care. Clinical trials have reported conflicting results when studying whether the colony-stimulating factors (CSFs) improve outcomes in patients with FN. This Cochrane Collaboration review was undertaken to further evaluate the safety and efficacy of the CSFs in patients with FN.

Methods

An exhaustive literature search was undertaken including major electronic databases (CANCERLIT, EMBASE, LILACS, MEDLINE, SCI, and the Cochrane Controlled Trials Register). All randomized controlled trials that compare CSFs plus antibiotics versus antibiotics alone for the treatment of established FN in adults and children were sought. A meta-analysis of the selected studies was performed.

Results

More than 8,000 references were screened, with 13 studies meeting eligibility criteria for inclusion. The overall mortality was not influenced significantly by the use of CSF (odds ratio [OR] = 0.68; 95% CI, 0.43 to 1.08; $P = .1$). A marginally significant result was obtained for the use of CSF in reducing infection-related mortality (OR = 0.51; 95% CI, 0.26 to 1.00; $P = .05$). Patients treated with CSFs had a shorter length of hospitalization (hazard ratio [HR] = 0.63; 95% CI, 0.49 to 0.82; $P = .0006$) and a shorter time to neutrophil recovery (HR = 0.32; 95% CI, 0.23 to 0.46; $P < .00001$).

Conclusion

The use of the CSFs in patients with established FN caused by cancer chemotherapy reduces the amount of time spent in hospital and the neutrophil recovery period. The possible influence of the CSFs on infection-related mortality requires further investigation.

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INTRODUCTION

Febrile neutropenia (FN) is a relatively frequent event in cancer patients treated with chemotherapy. It is a potentially life-threatening situation and requires prompt medical intervention.[1] The standard treatment includes supportive care plus broad-spectrum antibiotics.[1] There is no consensus in the literature as to which antibiotics or combination of antibiotics is best for these patients.[2] Hematopoietic growth-stimulating factors are a class of cytokines that regulate proliferation, differentiation, and functions of hematopoietic cells.[3] More than 20 different molecules of hematopoietic growth factors have been identified,[3] and many have been tested in clinical studies for different applications.[3,4]

Among them, the granulocyte colony-stimulating factor (G-CSF) and the granulocyte-macrophage colony-stimulating factor

(GM-CSF) have been studied in cancer patients because of their potential effect on neutropenia. G-CSF regulates the production of neutrophil lineage. The administration of G-CSF to humans results in a dose-dependent increase in circulating neutrophils[3,5] mainly because of a reduced transit time from stem cell to mature neutrophil.[3] GM-CSF stimulates the growth of granulocyte, macrophage, and eosinophil colonies.[3,5] Administration of GM-CSF to humans results in a dose-dependent increase in blood neutrophils, eosinophils, macrophages, and sometimes lymphocytes.[3,5] Different types of G-CSF and GM-CSF have been tested in clinical trials and are available on the market. Among the most used G-CSFs are filgrastim and lenograstim, and among the most used GM-CSFs are sargramostim and molgramostim.

Both G-CSF and GM-CSF have been demonstrated to be effective in reducing the incidence of FN when administered immediately after chemotherapy[6,7] and as supportive therapy in patients undergoing bone marrow transplantation.[5,3] The known effect of G-CSF and GM-CSF in increasing the number of circulating neutrophils provided the background for clinical studies designed to assess their role as adjunct therapy to antibiotics in FN patients. The results of randomized studies performed in this setting were not clear, and conflicting results appeared; two trials found no significant effect of colony-stimulating factors (CSFs) in the prevention of prolonged hospitalization,[8,9] whereas another study found a significant effect on length of hospitalization.[10] Time to recovery from fever seems to be favorably affected by CSF in some studies[11,12] but not in others.[13] Also, different results regarding the use of CSF are reported for patients who are classified according to their baseline risk as being at low or high risk for developing life-threatening complications.[11] Individually, these studies included less than 220 patients, and because of low rates of clinical events, such as death rates, and their small size, the studies may be underpowered to detect a difference between the treated groups. On the basis of the results of these randomized trials, the American Society of Clinical Oncology does not recommend the routine use of CSF in the treatment of FN.[14-17]

Conflicting results obtained from small studies demand the development of a systematic review of the literature[18] to build the totality of evidence for an informed medical decision. The systematic review reported here was designed to evaluate the safety and effectiveness of the addition of G-CSF or GM-CSF to standard treatment of FN related to chemotherapy.

METHODS

Types of Studies

Studies included all randomized controlled trials with a parallel design that compared the use of CSF plus antibiotics versus antibiotics alone for the treatment of established chemotherapy-induced FN.

Types of Participants

Participants were patients undergoing chemotherapy for cancer who experienced neutropenia (absolute neutrophil count [ANC] $< 1 \times 10^9$/L) and fever (body temperature > 38.5°C on one occasion or > 38°C on two or more occasions).

Types of Interventions

The types of interventions were G-CSF or GM-CSF plus antibiotics versus antibiotics alone.

Types of Outcome Measures

Outcome measures included overall and infection-related mortality, time of hospitalization, time to antibiotic withdrawal, time to neutrophil recovery, time to defervescence, and treatment side effects. A previous meta-analysis[19] detected an increased rate of deep vein thrombosis (DVT) among those patients receiving CSF; therefore, the occurrence of this side effect was studied as a separate end point.

Search Strategy for Identifying Studies

A wide search of the main computerized databases of interest was conducted, including CANCERLIT, EMBASE, LILACS, MEDLINE, SCI, and The Cochrane Controlled Trials Register. Experts in oncology and hematology were consulted about studies currently ongoing or that have not yet been published. Personal collections of articles of two of the authors (G.H.L. and B.D.) were also scanned. All references of relevant articles were scanned, and all additional articles of potential interest were retrieved for further analysis. For MEDLINE, we used the methodologic search strategy for randomized controlled trials[20] recommended by the Cochrane Collaboration.[21] For EMBASE, we used adaptations of this same strategy, and for LILACS, we used the methodologic search strategy reported by Castro et al.[22] We performed an additional search on the SCI database looking for studies that had cited the included studies. We added the specific terms pertinent to this review to the overall methodologic search strategy for each database.

The overall search strategy was as follows: (1) explode COLONY-STIMULATING-FACTORS/all subheadings; (2) CSF; (3) No. 1 OR No. 2; (4) explode FEVER/all subheadings; (5) FEVER* OR FEBR*; (6) No. 4 OR No. 5; (7) No. 3 AND No. 6; and (8) No. 1 AND No. 8. Two of the authors (O.A.C.C. and A.A.C.) reviewed the list of references and independently selected additional studies. Only studies representing randomized controlled trials of CSFs in cancer patients with established FN were selected for data extraction. Disagreements were resolved by a consensus meeting.

Critical Evaluation of the Selected Studies

Details regarding the main methodologic characteristics empirically linked to bias[18] were extracted, and the methodologic validity of each selected trial was assessed by two reviewers (O.A.C.C. and B.D.). Special attention was given to the generation and concealment of the sequence of randomization, blinding, whether an intent-to-treat analysis was performed, placebo use, and source of funding. These data were used in subgroup and sensitivity analyses to test the stability of our conclusions. We also analyzed subgroups according to the following clinical characteristics: use in children or adults, hematologic or solid tumors, CSF used, diagnostic criteria of neutropenia, and criteria for hospital discharge.

Table 1. Characteristics of Excluded Studies

Study	Reason for Exclusion
Balcerska et al[29]	Not randomized
Beveridge et al[30]	Studied nonfebrile patients and did not have a no-therapy group
Bodey et al[31]	Duplicate publication of Anaissie et al[8]
Feng and Zhou[32]	Cross-over study
Garcia-Carbonero et al[33]	Duplicate publication of Garcia-Carbonero et al[62]
Garcia-Carbonero et al[34]	Duplicate publication of Garcia-Carbonero et al[62]
Gebbia et al[35]	Included nonneutropenic patients; the treatment began immediately after chemotherapy
Gunay et al[36]	Not randomized
Herrmann et al[37]	Not randomized
Kaku et al[38]	Patients who had developed febrile neutropenia were randomly assigned to receive CSF just after the next cycle of chemotherapy
Kawa et al[39]	Randomized patients to receive CSF before or after the neutropenia developed
Kotake et al[40]	Not randomized
Mayordomo et al[41]	Duplicate publication of Garcia-Carbonero et al[62]
Mayordomo et al[42]	Duplicate publication of Garcia-Carbonero et al[62]
Michon et al[43]	Did not include patients with febrile neutropenia
Montalar et al[44]	Data not extractable
Moriyama et al[45]	Not randomized
Motoyoshi et al[46]	Cross-over trial
Nakajima et al[47]	Also included patients who had documented infection but were not neutropenic
Ohno et al[48]	Included nonneutropenic patients; the treatment began immediately after chemotherapy
Oshita et al[49]	Patients were randomly assigned to receive CSF after the development of monocytopenia or leukopenia
Ravaud et al[50]	Duplicate from Ravaud et al[11]
Schroder et al[51]	Not randomized
Soda et al[52]	Randomized patients to receive CSF before or after the neutropenia developed
Torrecillas et al[53]	Patients were randomly assigned to duration of CSF use
Uyl-de Groot et al[54]	Duplicate publication of Vellenga et al[13]
van Pelt et al[55]	Not neutropenic patients
Vellenga et al[56]	Duplicate publication of Vellenga et al[13]
Yalcin et al[57]	Not randomized
Yamazaki et al[58]	Not neutropenic patients

Abbreviation: CSF, colony-stimulating factor.

Data Extraction

Two investigators (O.A.C.C. and B.D.) independently extracted the data from the articles. The name of the first author and the publication year were used for identification purposes. All data were extracted directly from the text or, when possible, calculated according to the available information. Data on the selected clinical outcomes and methodologic characteristics and additional data on the types of participants in each study were retrieved. When time-to-event data were not available for direct extraction, we extracted data according to the method described by Parmar et al.[23] This method permits the indirect calculation of the variance and the number of observed minus expected events from many different parameters. To allow representation in RevMan 4.1 (Cochrane Collaboration, Oxford, United Kingdom), time to event data were entered as aggregate data under individual patient data entry.

Outcome Measures

Clinical outcome measures included overall and infection-related mortality, length of hospitalization, time to neutrophil recovery, time to resolution of fever, time to withdrawal of antibiotics, and adverse effects including DVT. Additional covariates extracted from the studies included the following: adults or children; diagnostic criteria of neutropenia (ANC); antibiotics used; treatment schedule and CSF used; type of tumor (solid or hematologic); number of patients included, excluded, and analyzed; analysis per protocol or by intent-to-treat; source of funding; and criteria for hospital discharge. All disagreements were resolved by consensus conference.

Analysis and Presentation of Results

For dichotomous outcomes, such as overall and infection-related mortality, summary estimates and variance expressed as 95% confidence intervals were calculated by the method of Peto based on a fixed effects model.[24] When the pooled results were significant, the number of patients needed to treat to cause or to prevent one event was calculated.[25] For time to event data, such as duration of hospitalization and time to neutrophil recovery, the observed minus expected log-rank statistics plus the variance were calculated by the methods described by Parmar et al.[23] The pooled results represent the hazard ratio (HR).[23] Statistical heterogeneity in the results of the trials was assessed to check whether the differences among the results of trials were greater than what could be expected by chance alone. This was done by looking at the graphical display of the results and by using the χ^2 test of heterogeneity described by DerSimonian and Laird.[26] When significant heterogeneity was found, a possible explanation was intensively sought. If a reasonable cause was found, a separate analysis was performed. If the cause was not apparent, and heterogeneity was caused by divergent data in terms of direction of results (ie, data

Table 2. Characteristics of Included Studies

Study	Methods	Participants	Interventions	Outcomes	Concealment
Anaissie et al[8]	Random: y Blind: n Withdrawals: y Size: n ITT: y Pla: n Multicenter: n Funding: i	Adults; mixed tumors; ANC $< 1 \times 10^9$/L	GM-CSF (molgrastim, Sandoz) 3μg/kg IV	Overall mortality; infection-related mortality; length of hospitalization	B
Arnberg et al[59]	Random: n Blind: y Withdrawals: y Size: n ITT: y Pla: y Multicenter: n Funding: m	Adults; mixed tumors; ANC $< 1 \times 10^9$/L	GM-CSF (not specified) 5.5 μg/kg SC	Overall mortality; bone and joint pain or flu-like symptoms	B
Aviles et al[60]	Random: y Blind: n Withdrawals: y Size: n ITT: n Pla: n Multicenter: n Funding: u	Adults; hematologic tumors; ANC $< 0.1 \times 10^9$/L	G-CSF (not specified) 5 μg/kg SC	Overall mortality; infection-related mortality	A
Biesma et al[61]	Random: n Blind: y Withdrawals: y Size: n ITT: n Pla: y Multicenter: n Funding: i	Adults; mixed tumors; ANC $< 1 \times 10^9$/L	GM-CSF (not specified) 2.8 μg/kg IV	Overall mortality; infection-related mortality; deep vein thrombosis	B
Garcia-Carbonero et al[62]	Random: y Blind: n Withdrawals: y Size: y ITT: y Pla: n Multicenter: y Funding: m	Adults; mixed tumors; ANC $< 0.5 \times 10^9$/L	G-CSF (not specified) 5 μg/kg SC	Overall mortality; infection-related mortality; length of hospitalization; deep vein thrombosis	A
Lopez-Hernandez et al[63]	Random: y Blind: n Withdrawals: y Size: n ITT: n Pla: n Multicenter: n Funding: u	Adults and children; hematologic tumors; ANC $< 0.5 \times 10^9$/L	G-CSF (filgrastim) 5 μg/kg SC	Overall mortality; infection-related mortality	B
Maher et al[9]	Random: n Blind: y Withdrawals: y Size: y ITT: y Pla: y Multicenter: y Funding: i	Adults; mixed tumors; ANC $< 1 \times 10^9$/L	G-CSF (filgrastim) 12 μg/kg SC	Overall mortality; length of hospitalization; bone and joint pain or flu-like symptoms	A
Mayordomo et al[12]	Random: n Blind: n Withdrawals: y Size: y ITT: y Pla: y Multicenter: n Funding: i	Adults; mixed tumors; ANC $< 0.5 \times 10^9$/L	G-CSF (filgrastim) 5 μg/kg IV or GM-CSF (molgramostim) 5 μg/kg IV	Overall mortality; infection-related mortality; length of hospitalization; bone and joint pain or flu-like symptoms	A
Mitchell et al[64]	Random: n Blind: y Withdrawals: y Size: y ITT: y Pla: y Multicenter: y Funding: i	Children; mixed tumors; ANC $< 0.5 \times 10^9$/L	G-CSF (filgrastim) 5 μg/kg IV	Overall mortality; length of hospitalization	A

(continued on following page)

Table 2. Characteristics of Included Studies (continued)

Study	Methods	Participants	Interventions	Outcomes	Concealment
Ravaud et al[11]	Random: n Blind: n Withdrawals: y Size: y ITT: y Pla: n Multicenter: y Funding: i	Adults; solid tumors; ANC $< 1 \times 10^9$/L	GM-CSF (molgramostim) 5 μg/kg SC	Overall mortality; infection-related mortality; bone and joint pain or flu-like symptoms	B
Riikonen et al[10]	Random: y Blind: y Withdrawals: y Size: n ITT: n Pla: y Multicenter: y Funding: a	Children; mixed tumors; ANC $< 0.2 \times 10^9$/L	GM-CSF (Sandoz) 5 μg/kg IV	Overall mortality; infection-related mortality; length of hospitalization; bone and joint pain or flu-like symptoms	B
Vellenga et al[13]	Random: y Blind: y Withdrawals: y Size: y ITT: y Pla: y Multicenter: y Funding: m	Adults; mixed tumors; ANC $< 0.5 \times 10^9$/L	GM-CSF (Sandoz) 5 μg/kg SC	Overall mortality; infection-related mortality; length of hospitalization; deep vein thrombosis; bone and joint pain or flu-like symptoms	B
Yoshida et al[65]	Random: y Blind: n Withdrawals: y Size: n ITT: y Pla: n Multicenter: y Funding: u	Adults; hematologic tumors; ANC $< 1 \times 10^9$/L	G-CSF (filgrastim or lenograstim) variable doses, IV	Length of hospitalization	B

Abbreviations: Random, adequate method of randomization described; Blind, double-blind study; Withdrawals, withdrawals described; Size, sample size preplanned; ITT, intent-to-treat analysis; Pla, placebo used; Multicenter, multicenter study; Funding, source of funding; y, yes; n, no; i, industry; a, academic; m, mixed; u, unclear; ANC, absolute neutrophil count; IV, intravenous; SC, subcutaneous; GM-CSF, granulocyte-macrophage colony-stimulating factor; G-CSF, granulocyte colony-stimulating factor.

favoring one or another treatment), we chose not to pool the data. Where appropriate, studies were pooled in a meta-analysis using the RevMan 4.1.1. To assess the possibility of publication bias,[18] we performed the funnel plot test described by Egger et al.[27] Although there is no universally agreed on method for estimating statistical power in a meta-analysis, a conventional, large sample, normal approximation (z test) difference in two proportions with a type I error rate of less than 0.05 in a single randomized controlled trial provides a reasonable upper bound on meta-analysis power estimates for observed differences in event rates.[28] Therefore, power estimates provided representative overestimates of the true power of such analyses.

RESULTS

Final Studies Selected

Overall, more than 8,000 references were identified and scanned. Forty-four studies were selected and retrieved for full-text analysis. Of these studies, 22 were excluded for various reasons (Table 1). Of the 22 randomized trials that fit inclusion criteria, eight were duplicate reports or early publications in abstract format. Fourteen original reports of trials on the role of CSF in established FN, with a total of 1,569 patients, were included in the final analysis (Table 2). One of these trials was published in abstract form only,[43] and no information on the outcomes was available. We tried to contact the authors of this abstract by e-mail but received no response. Therefore, this trial was excluded from our analysis. This trial included a total of 51 patients, and its inclusion would have had a low potential to alter the results. Therefore, our analysis relates to 13 studies. Six articles described the effects of G-CSF, six described the effects of GM-CSF, and one[12] was a three-arm study in which patients were randomly assigned to G-CSF, GM-CSF, or placebo. This multiarm study was approached in different ways: first, each CSF arm was compared with the control arm. In the second analysis, the two active arms were combined, by adding all CSF-treated patients, and analyzed against the control. Both analyses achieved virtually the same results, and we will refer to the results of the second method in the text. The results of the first analysis are available under the subgroup analysis graphs G-CSF versus GM-CSF. Six articles included patients with ANCs less than 1×10^9/L; five articles included patients with ANCs less than 0.5×10^9/L; one article included patients

Table 3. Comparisons and Data: Main Analysis—CSF + ATB vs ATB Alone

Study	CSF + ATB (No.)	CSF + ATB (No.)	ATB Alone (No.)	ATB Alone (No.)	O − E	Variance
Overall mortality						
Anaissie et al[8]	3	50	3	50	—	—
Arnberg et al[59]	1	14	0	15	—	—
Aviles et al[60]	5	61	15	61	—	—
Biesma et al[61]	1	12	0	14	—	—
Garcia-Carbonero et al[62]	4	104	5	99	—	—
Lopez-Hernandez et al[63]	1	21	2	19	—	—
Maher et al[9]	12	109	15	107	—	—
Mayordomo et al[12]	6	78	2	43	—	—
Mitchell et al[64]	0	94	0	92	—	—
Ravaud et al[11]	0	34	1	34	—	—
Riikonen et al[10]	0	28	0	30	—	—
Vellenga et al[13]	1	65	2	69	—	—
Infection-related mortality						
Anaissie et al[8]	1	50	3	50	—	—
Aviles et al[60]	5	61	15	61	—	—
Biesma et al[61]	1	12	0	14	—	—
Garcia-Carbonero et al[62]	3	104	2	99	—	—
Lopez-Hernandez et al[63]	1	21	2	19	—	—
Mayordomo et al[12]	3	78	1	43	—	—
Ravaud et al[11]	0	34	1	34	—	—
Riikonen et al[10]	0	28	0	30	—	—
Vellenga et al[13]	0	65	0	69	—	—
Length of hospitalization						
Anaissie et al[8]	18	50	26	50	−4.00	6.22
Garcia-Carbonero et al[62]	24	104	23	99	−0.08	9.07
Maher et al[9]	30	109	52	107	−11.38	12.78
Mayordomo et al[12]	3	78	15	43	−8.60	3.54
Mitchell et al[64]	17	94	18	92	−0.69	7.14
Riikonen et al[10]	7	28	15	30	−3.62	3.47
Vellenga et al[13]	6	65	7	69	−0.31	2.95
Yoshida et al[65]	39	102	33	101	2.82	11.67
Time to neutrophil recovery						
Garcia-Carbonero et al[62]	2	104	6	99	−2.10	1.93
Maher et al[9]	31	109	58	107	−13.91	13.14
Mayordomo et al[12]	0	78	9	43	−5.80	1.92
Mitchell et al[64]	58	94	71	92	−7.19	9.94
Ravaud et al[11]	14	34	26	34	−6.00	4.18
Deep vein thrombosis						
Arnberg et al[59]	1	14	0	15	—	—
Biesma et al[61]	6	11	4	12	—	—
Garcia-Carbonero et al[62]	0	104	1	99	—	—
Vellenga et al[13]	2	65	0	69	—	—
Bone and joint pain or flu-like symptoms						
Arnberg et al[59]	0	14	0	15	—	—
Maher et al[9]	33	109	24	107	—	—
Mayordomo et al[12]	5	78	0	43	—	—
Ravaud et al[11]	4	34	0	34	—	—
Riikonen et al[10]	4	28	0	30	—	—
Vellenga et al[13]	1	65	1	65	—	—

Abbreviations: CSF, colony-stimulating factor; ATB, antibiotics; O − E, observed − expected.

with ANCs less than 0.2×10^9/L; and one article included patients with ANCs less than 0.1×10^9/L. Ten articles enrolled adults, two enrolled children, and one included both. Three articles enrolled patients with hematologic tumors only, one article included solid tumors only, and nine articles included patients with either category of malignancy.

Randomization of Patients Versus Episodes

A particular problem identified in trials of FN was that of rerandomization.[64] This practice has the potential to bias results of clinical trials because of the possible dependence of outcomes on the previous events. Patients who have already developed one episode of FN are expected to be more prone to develop another, which in turn, may violate

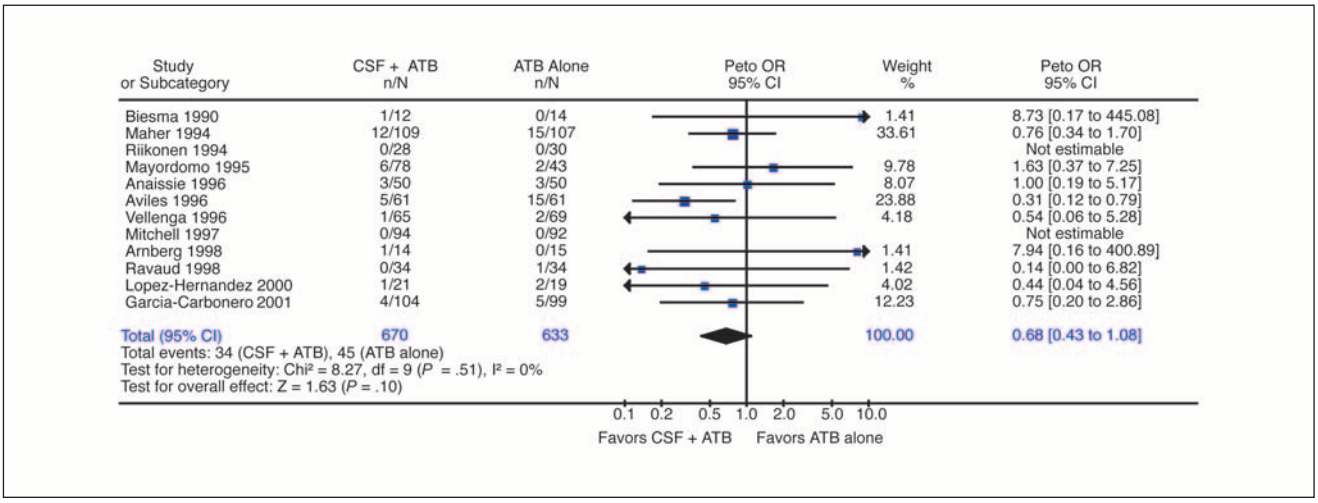

Fig 1. Colony-stimulating factors (CSF) for the treatment of chemotherapy-induced febrile neutropenia. Comparison: CSF plus antibiotics (ATB) versus ATB alone. Outcome: mortality. OR, odds ratio.

an assumption that all events must be independent of each other to allow proper analysis of a trial as well as pooling data in a meta-analysis.[65] Four trials[8,10,61,62] allowed patients to be entered onto the study and randomized more than once. These trials analyzed 384 episodes and are responsible for approximately one quarter of the total number of episodes and patients included in this systematic review. It was impossible to extract data from these trials according to the number of patients. Because the rerandomization practice is allowed by the Immunocompromised Host Society,[66] we included these trials in our analysis. A sensitivity analysis addressed this question further.

Methodologic Validity of Included Studies

Seven of the included articles described an adequate method of randomization,[8,10,13,60,62,63,65] and five reported an adequate concealment of the sequence of allocation.[9,12,60,62,64] Six trials were double blinded,[9,10,13,59,61,64] and seven were placebo controlled.[9,10,12,13,59,61,64] A sample size was preplanned in six trials,[9,11-13,62,64] but the planned number was not reached in one trial.[11] An intent-to-treat analysis was performed in nine articles,[8,9,11-13,59,62,64,65] and seven articles referred to multicentric studies.[9-11,13,62,64,65] One of the studies[60] had a high rate of mortality in the no treatment group. Concerns regarding the comparability of the study arms of this trial[60] were raised in the literature[66] because of large differences in mortality rates reported between the two groups studied and the lack of description of important baseline characteristics of the patients in the groups. Therefore, we decided to perform our analysis both with and without this trial.

Final Analysis

The final analysis included 13 trials with a total of 1,518 patients. Seven hundred seventy-nine patients were randomly assigned to CSF, and 739 were assigned to the control

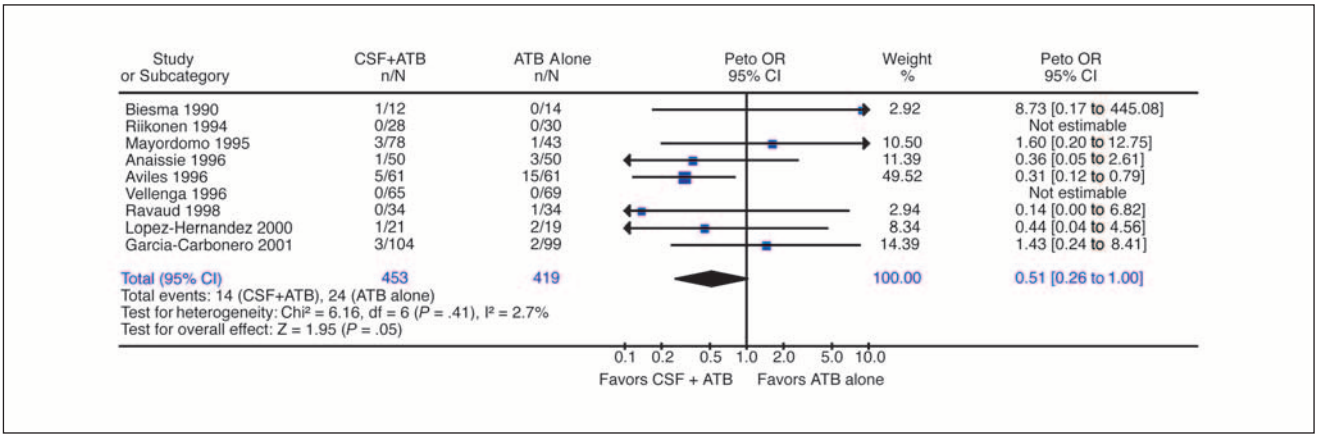

Fig 2. Colony-stimulating factors (CSF) for the treatment of chemotherapy-induced febrile neutropenia. Comparison: CSF plus antibiotics (ATB) versus ATB alone. Outcome: infection-related mortality. OR, odds ratio.

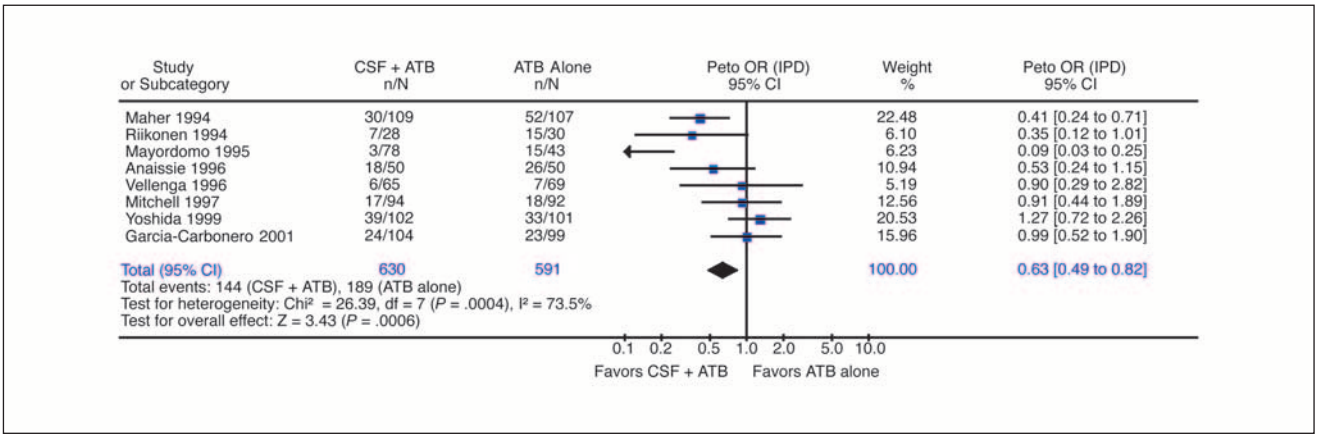

Fig 3. Colony-stimulating factors (CSF) for the treatment of chemotherapy-induced febrile neutropenia. Comparison: CSF plus antibiotics (ATB) versus ATB alone. Outcome: length of hospitalization. OR, odds ratio; IPD, individual patient data.

group (antibiotics plus no treatment or placebo). Not all articles allowed data extraction for all end points (Table 3).

Overall mortality. Data on overall mortality could be extracted from 12 trials with 1,303 patients. There were 34 deaths among 670 patients randomly assigned to CSF and 45 deaths among the 633 patients assigned to the control group. No heterogeneity was detected in the analysis ($\chi^2 = 8.27$; $df = 9$; $P = .51$). The meta-analysis showed a trend in favor of CSF use, but it did not reach statistical significance (odds ratio [OR] = 0.68; 95% CI, 0.43 to 1.08; $P = .10$; Fig 1). The trend to benefit patients receiving CSF completely disappeared when we excluded from the analysis the trial published by Aviles et al[60] (OR = 0.87; 95% CI, 0.51 to 1.49; $P = .6$). This trial included only patients with hematologic malignancies and was responsible for a high rate of events in the control group (15 of 64 patients died). These 15 deaths represent 33% of the total deaths (15 of 45 deaths) in the control group among all trials. However, the upper bound estimate on the power of the meta-analysis of all studies to show a reduction in overall mortality with CSFs of the magnitude observed or greater is only 33%.

Infection-related mortality. Data on infection-related mortality from nine trials with 872 patients was obtained. There were 14 infection-related deaths among the 453 patients randomly assigned to CSF and 24 infection-related deaths among the 419 patients assigned to control groups. No heterogeneity was detected for this outcome ($\chi^2 = 6.16$; $df = 6$; $P = .4$). The meta-analysis showed a borderline significant benefit in favor of CSF use (OR = 0.51; 95% CI, 0.26 to 1.00; $P = .05$; Fig 2). This benefit also completely disappeared when we excluded the Aviles et al[60] trial (OR = 0.85; 95% CI, 0.33 to 2.20; $P = .7$). For this end point, the impact of this trial alone was even higher; 63% of the events (15 of 24 events) in the control group were reported by this trial. The upper bound estimate on the power of the meta-analysis of all studies to show a reduction in infection-related mortality with CSFs of the magnitude observed or greater is 66%. Although the estimated ORs for infection-related mortality separately for G-CSF (OR = 0.52; 95% CI, 0.24 to 1.09) and GM-CSF (OR = 0.63; 95% CI, 0.15 to 2.55) are not statistically

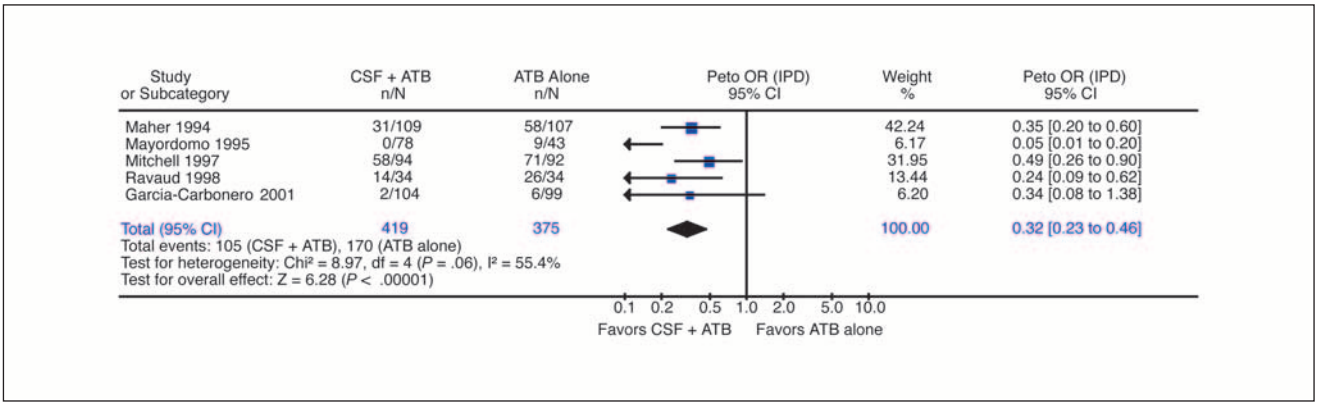

Fig 4. Colony-stimulating factors (CSF) for the treatment of chemotherapy-induced febrile neutropenia. Comparison: CSF plus antibiotics (ATB) versus ATB alone. Outcome: time to neutrophil recovery. OR, odds ratio; IPD, individual patient data.

significant, the upper bound estimates on power for these study subgroups were only 40% and 10%, respectively.

Length of hospitalization. Data on length of hospitalization was available from eight trials that included 1,221 patients. Significant heterogeneity was observed by the χ^2 test ($\chi^2 = 26.39$; $df = 7$; $P = .0004$). The meta-analysis of all the trials showed a benefit in favor of CSF use (HR = 0.63; 95% CI, 0.49 to 0.82; $P = .0006$; Fig 3). As planned, we explored the possible causes of heterogeneity to determine whether it was appropriate to pool the trials. All trials but one[63] had an effect estimate that favored CSF, although only two reached statistical significance. By inspecting the graphs, we could detect that the Mayordomo et al[12] trial indicated a much stronger effect than that detected in all other trials. Therefore, we repeated our analysis excluding this trial.[12] The exclusion resulted in substantial reduction in heterogeneity ($\chi^2 = 11.67$; $df = 6$; $P = .07$), and the significance of the treatment effect remained (HR = 0.72; 95% CI, 0.55 to 0.95; $P = .02$). Considering that all but one study favored the use of CSF and that the heterogeneity detected was mainly the result of a higher effect of CSF detected by one trial, the results reported here are consistent with a significant effect of CSF in reducing the length of hospitalization. However, because of significant heterogeneity, the magnitude of this effect cannot be precisely estimated with currently available data.

Time to neutrophil recovery. From five trials, data on a total of 794 patients with regard to time to neutrophil recovery were extracted. A significant effect of CSF was observed (HR = 0.32; 95% CI, 0.23 to 0.46; $P < .0001$) with a small statistical heterogeneity ($\chi^2 = 8.97$; $df = 4$; $P = .062$; Fig 4). Again, this heterogeneity was largely a result of the magnitude of the CSF effect detected in the Mayordomo et al[12] trial. When we excluded this trial from the analysis, the effect was maintained (HR = 0.37; 95% CI, 0.26 to 0.53; $P < .00001$), and the heterogeneity disappears ($\chi^2 = 1.61$; $df = 3$; $P = .66$). Estimate points favored the use of CSF, and in all but one trial,[60] the studies were statistically significant. So, despite the small heterogeneity detected in the overall analysis, we can conclude that CSF is effective in reducing the time to neutrophil recovery.

Time to recovery from fever and time to withdrawal from antibiotics. The time to recovery from fever and time to withdrawal from antibiotics were poorly reported among the included trials; the data could be extracted in a reliable condition from only one study each, Maher et al[9] and García-Carbonero et al,[62] respectively. Therefore, we were unable to pool these data. We chose to report only the medians of these end points reported in the studies.

Side effects. There was a huge difference in the methods used by the authors to report side effects. We could extract data from the articles about two side effects only, DVT and adverse events related to bone pain, joint pain, and flu-like symptoms. The number of patients developing DVT could be extracted from four studies with 389 patients. There were nine cases of DVT among 194 patients randomly assigned to CSF and five cases among 195 controls. The difference between the groups was not significant (OR = 2.49; 95% CI, 0.72 to 8.66; $P = .15$), and no heterogeneity was detected ($\chi^2 = 3.2$; $df = 3$; $P = .36$). Bone pain, joint pain, and flu-like symptoms could be extracted from six studies with 622 patients. Forty-seven patients developed these symptoms from 328 patients randomly assigned to CSF, and 25 patients developed these symptoms from 294 controls. The difference between the groups was significant and favored the controls (OR = 2.05; 95% CI, 1.22 to 3.46; $P = .007$; Fig 5). No heterogeneity was detected ($\chi^2 = 6.03$; $df = 4$; $P = .2$). This result means that one in 14 patients treated with CSF (95% CI, 9 to 50 patients) will experience one of these symptoms.

Subgroup Analysis

A number of subgroup analyses were performed (Table 4). Subgroup analyses according to the type of CSF (G-CSF and GM-CSF only) are presented (Figs 6, 7, 8, and 9). The only outcome that was affected by the type of CSF used was

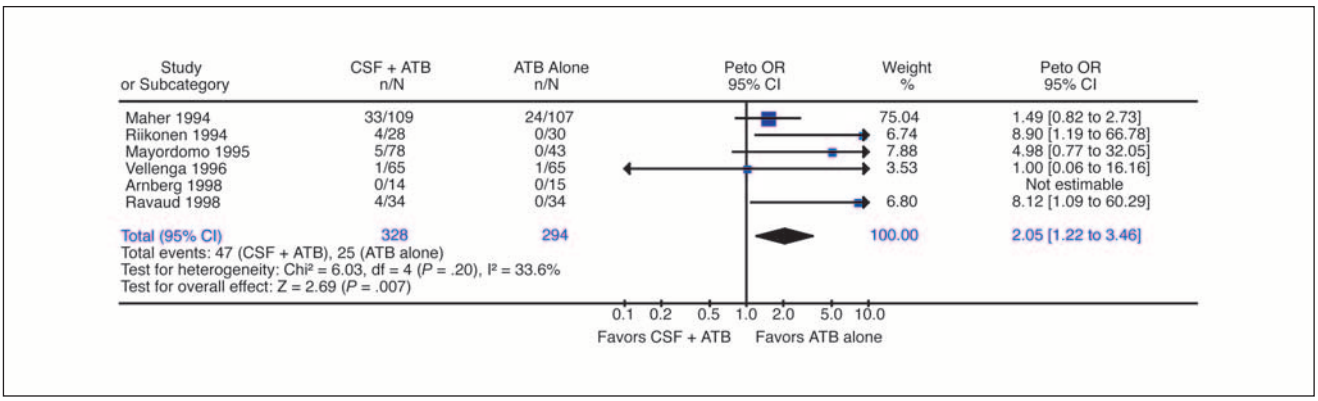

Fig 5. Colony-stimulating factors (CSF) for the treatment of chemotherapy-induced febrile neutropenia. Comparison: CSF plus antibiotics (ATB) versus ATB alone. Outcome: bone and joint pain or flu-like syndrome. OR, odds ratio.

Table 4. Subgroup Analysis: G-CSF and GM-CSF

Study	CSF + ATB (No.)	CSF + ATB (No.)	ATB Alone (No.)	ATB Alone (No.)	O − E	Variance
Mortality						
G-CSF						
Aviles et al[60]	5	61	15	61	—	—
Garcia-Carbonero et al[62]	4	104	5	99	—	—
Lopez-Hernandez et al[63]	1	21	2	19	—	—
Maher et al[9]	12	109	15	107	—	—
Mayordomo et al[12]	4	39	2	43	—	—
Mitchell et al[64]	0	94	0	92	—	—
GM-CSF						
Anaissie et al[8]	3	50	3	50	—	—
Arnberg et al[59]	1	14	0	15	—	—
Biesma et al[61]	1	12	0	14	—	—
Mayordomo et al[12]	2	39	2	43	—	—
Ravaud et al[11]	0	34	1	34	—	—
Riikonen et al[10]	0	28	0	30	—	—
Vellenga et al[13]	1	65	2	69	—	—
Infection-related mortality						
G-CSF						
Aviles et al[60]	5	61	15	61	—	—
Garcia-Carbonero et al[62]	3	104	2	99	—	—
Lopez-Hernandez et al[63]	1	21	2	19	—	—
Mayordomo et al[12]	2	39	1	43	—	—
GM-CSF						
Anaissie et al[8]	1	50	3	50	—	—
Arnberg et al[59]	0	1	0	1	—	—
Biesma et al[61]	1	12	0	14	—	—
Mayordomo et al[12]	1	39	1	43	—	—
Ravaud et al[11]	0	34	1	34	—	—
Riikonen et al[10]	0	28	0	30	—	—
Vellenga et al[13]	0	65	0	69	—	—
Length of hospitalization						
G-CSF						
Garcia-Carbonero et al[62]	24	104	23	99	−0.08	9.07
Maher et al[9]	30	109	52	107	−11.38	12.78
Mayordomo et al[12]	1	39	15	43	−6.61	3.25
Mitchell et al[64]	17	94	18	92	−0.69	7.14
Yoshida et al[65]	39	102	33	101	2.82	11.67
GM-CSF						
Anaissie et al[8]	18	50	26	50	−4.00	6.22
Mayordomo et al[12]	2	39	15	43	−6.09	3.40
Riikonen et al[10]	7	28	15	30	−3.62	3.47
Vellenga et al[13]	6	65	7	69	−0.31	2.95
Time to neutrophil recovery						
G-CSF						
Garcia-Carbonero et al[62]	2	104	6	99	−2.10	1.93
Maher et al[9]	31	109	58	107	−13.91	13.14
Mayordomo et al[12]	0	39	9	43	−4.28	2.02
Mitchell et al[64]	58	94	71	92	−7.19	9.94
GM-CSF						
Mayordomo et al[12]	0	39	9	43	0.00	0.00
Ravaud et al[11]	14	34	26	34	−6.00	4.18
Deep vein thrombosis						
G-CSF						
Garcia-Carbonero et al[62]	0	104	1	99	—	—
GM-CSF						
Arnberg et al[59]	1	14	0	15	—	—
Biesma et al[61]	6	11	4	12	—	—
Vellenga et al[13]	2	65	0	69	—	—
Bone and joint pain or flu-like symptoms						
G-CSF						
Arnberg et al[59]	0	14	0	15	—	—
Mayordomo et al[12]	1	39	0	43	—	—

(continued on following page)

Table 4. Subgroup Analysis: G-CSF and GM-CSF (continued)

Study	CSF + ATB (No.)	CSF + ATB (No.)	ATB Alone (No.)	ATB Alone (No.)	O − E	Variance
GM-CSF						
Arnberg et al[59]	0	14	0	15	—	—
Mayordomo et al[12]	4	39	0	43	—	—
Ravaud et al[11]	4	34	0	34	—	—
Riikonen et al[10]	4	28	0	30	—	—
Vellenga et al[13]	1	65	1	65	—	—

Abbreviations: CSF, colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; G-CSF, granulocyte colony-stimulating factor; ATB, antibiotics; O − E, observed − expected.

the occurrence of side effects of bone pain, joint pain, and flu-like symptoms. Patients treated with GM-CSF had a higher likelihood of developing side effects (OR = 6.27; 95% CI, 2.15 to 18.28; $P = .0008$). Only one episode of these symptoms was reported among the 53 patients receiving G-CSF who were available for this analysis. No differences for other end points relating to the type of CSF were detected. These comparisons are indirect and, consequently, not extremely reliable because patients were not randomly assigned to G-CSF or GM-CSF in the same study except in the trial by Mayordomo et al.[12] Two of the three studies that included patients with hematologic malignancies reported mortality data. The subgroup analysis of the outcomes of overall mortality and infection-related mortality showed that patients with hematologic tumors showed a significant benefit of adding CSF (OR = 0.32; 95% CI, 0.13 to 0.78; $P = .01$), but this result is mainly because of the results of the Aviles et al[60] trial, which included 122 of 182 of these patients and reported 15 of the 17 deaths in the control group. Further subgroup and sensitivity analysis of overall and infection-related mortality data revealed no significant impact on the treatment effect of the CSFs. Specifically, the reported use of empiric cephalosporin, aminoglycoside, or a combination had no discernible effect on the CSF treatment effect.

For subgroup and sensitivity analysis related to the outcomes time of hospitalization and time to neutrophil recovery, the results were consistent among the trials and did not differ from the overall analysis. The only exception was the analysis of the length of hospitalization data

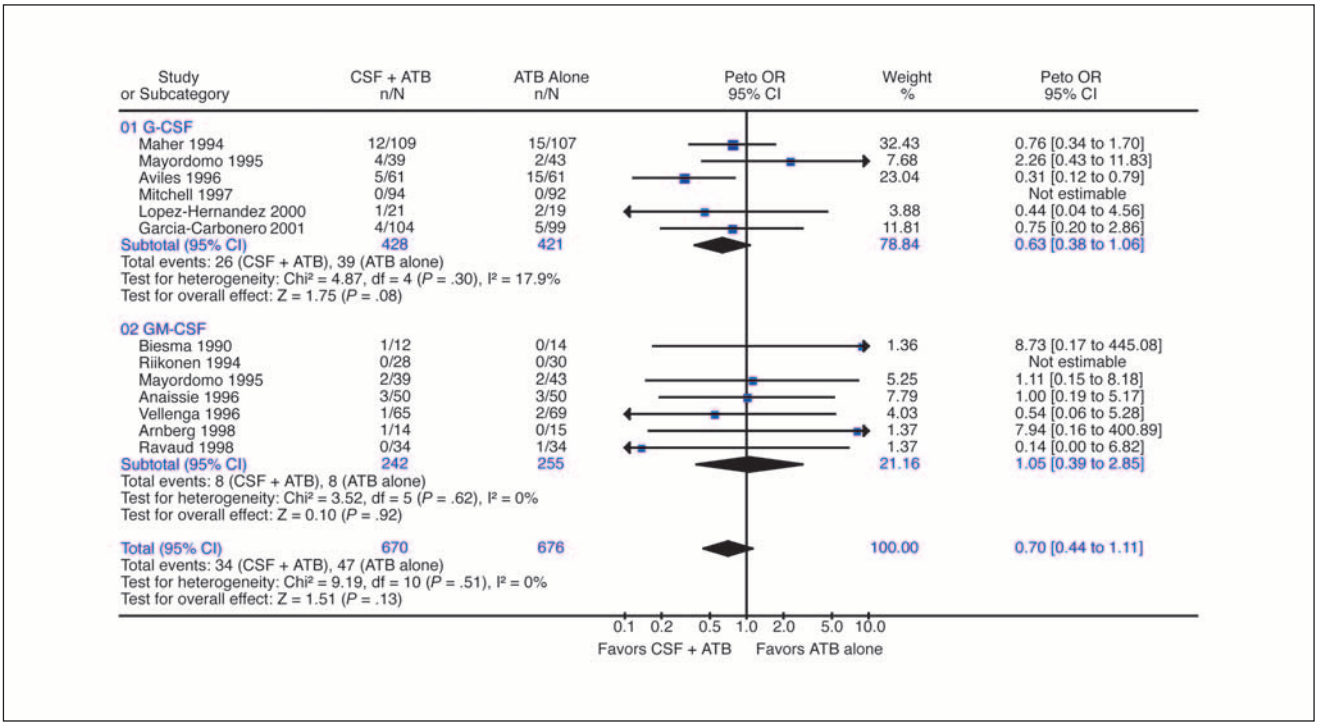

Fig 6. Colony-stimulating factors (CSF) for the treatment of chemotherapy-induced febrile neutropenia. Comparison: subgroup analysis, granulocyte CSF (G-CSF) and granulocyte-macrophage CSF (GM-CSF). Outcome: mortality. OR, odds ratio; ATB, antibiotics.

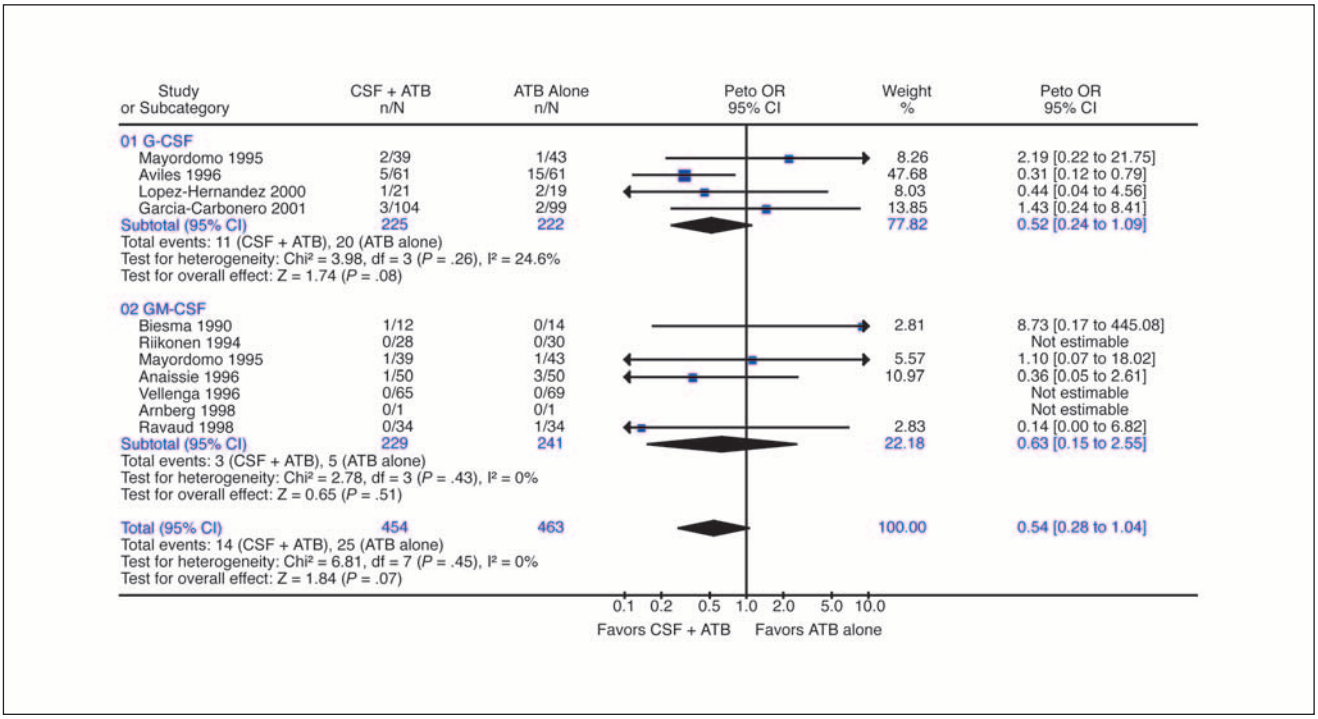

Fig 7. Colony-stimulating factors (CSF) for the treatment of chemotherapy-induced febrile neutropenia. Comparison: subgroup analysis, granulocyte CSF (G-CSF) and granulocyte-macrophage CSF (GM-CSF). Outcome: infection-related mortality. OR, odds ratio; ATB, antibiotics.

in children, where no difference was detected, although this analysis is based on only two trials. The subgroup analyses for the length of hospitalization in trials with an adequate allocation concealment and for double-blind trials were also significant and favored the group that received CSF compared with the no CSF group (HR = 0.66; 95% CI, 0.46 to 0.95 and HR = 0.54; 95% CI, 0.37 to 0.8, respectively).

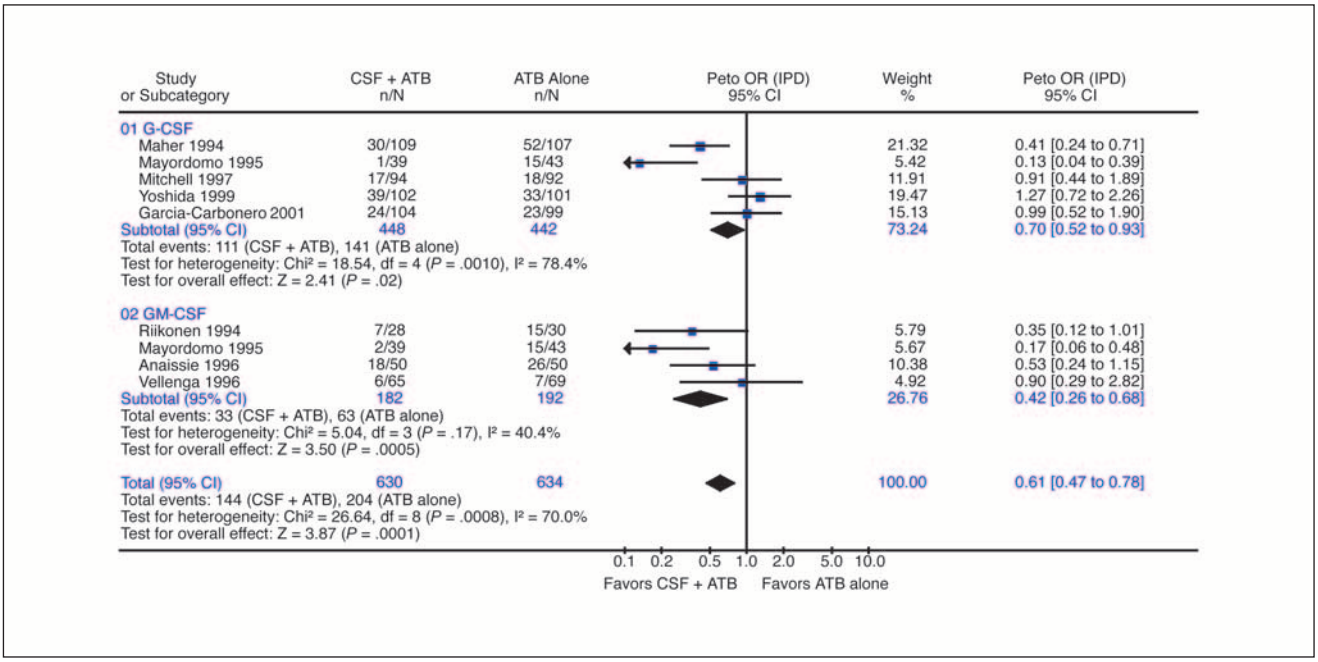

Fig 8. Colony-stimulating factors (CSF) for the treatment of chemotherapy-induced febrile neutropenia. Comparison: subgroup analysis, granulocyte CSF (G-CSF) and granulocyte-macrophage CSF (GM-CSF). Outcome: length of hospitalization. OR, odds ratio; ATB, antibiotics; IPD, individual patient data.

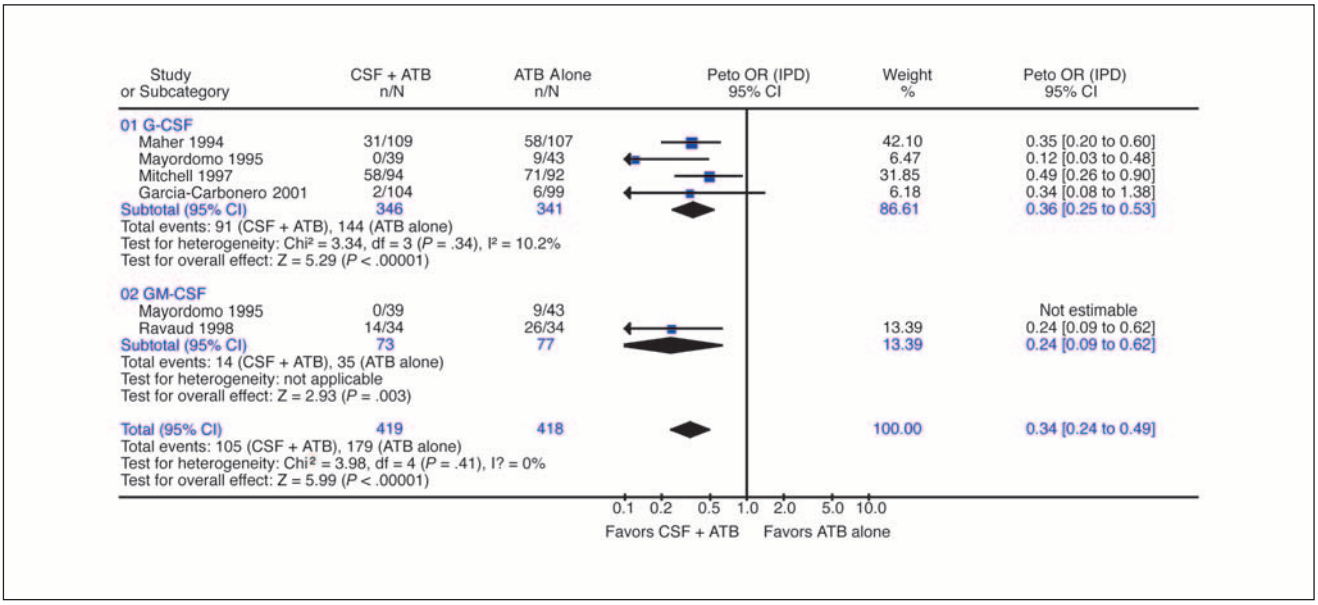

Fig 9. Colony-stimulating factors (CSF) for the treatment of chemotherapy-induced febrile neutropenia. Comparison: subgroup analysis, granulocyte CSF (G-CSF) and granulocyte-macrophage CSF (GM-CSF). Outcome: time to neutrophil recovery. OR, odds ratio; ATB, antibiotics; IPD, individual patient data.

We tested a possible effect of the criteria for hospital release on the effects of CSF in the duration of hospitalization (Table 5; Fig 10). There were no detectable differences in the required criteria to hospital release (time since defervescence and/or level of neutrophils) in the end points (Fig 11).

A planned subgroup analysis according to baseline risk based on neutrophil count at the time of admission was planned but could not be completed based on a priori study methodology. Only two trials included defined high risks,[10,60] and there were no deaths in one of them.[10]

Table 5. Influence of the Criteria to Hospital Discharge

Study	CSF + ATB (No.)	CSF + ATB (No.)	ATB Alone (No.)	ATB Alone (No.)	O − E	Variance
Length of hospitalization, influence of the criteria to hospital discharge						
Discharge after 48 hours of resolution of the fever						
Garcia-Carbonero et al[62]	24	104	23	99	−0.08	9.07
Mayordomo et al[12]	3	78	15	43	−8.60	3.54
Discharge after 72 hours of the resolution of the fever						
Mitchell et al[64]	17	94	18	92	−0.69	7.14
Riikonen et al[10]	7	28	15	30	−3.62	3.47
Vellenga et al[13]	6	65	7	69	−0.31	2.95
Discharge after 96 hours of the resolution of the fever						
Maher et al[9]	30	109	52	107	−11.38	12.78
ANC						
ANC > 200						
Mitchell et al[64]	17	94	18	92	−0.69	7.14
ANC > 500						
Maher et al[9]	30	109	52	107	−11.38	12.78
Riikonen et al[10]	7	28	15	30	−3.62	3.47
ANC > 1,000						
Garcia-Carbonero et al[62]	24	104	23	99	−0.08	9.07
Mayordomo et al[12]	3	78	15	43	−8.60	3.54
Vellenga et al[13]	6	65	7	69	−0.31	2.95

Abbreviations: CSF, colony-stimulating factor; ATB, antibiotics; ANC, absolute neutrophil count; O − E, observed − expected.

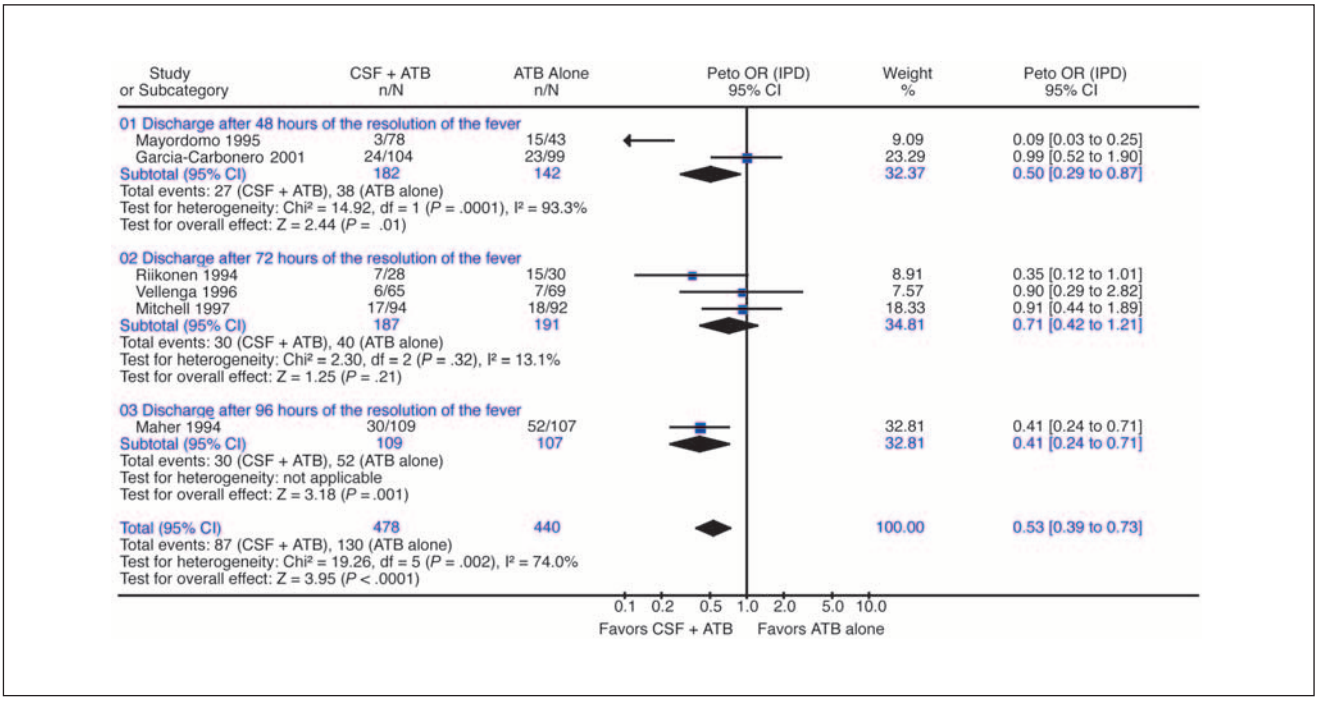

Fig 10. Colony-stimulating factors (CSF) for the treatment of chemotherapy-induced febrile neutropenia. Comparison: influence of the criteria of hospital discharge on the possible effects of CSF. Outcome: length of hospitalization, influence of the criteria to hospital discharge. OR, odds ratio; ATB, antibiotics; IPD, individual patient data.

DISCUSSION

This systematic review has attempted to address the totality of the evidence on the use of CSFs in cancer patients hospitalized with established FN caused by chemotherapy. Overall mortality seems not to be affected by the addition of CSF to antibiotics, whereas a borderline effect is observed on infection-related mortality. As noted, however, this

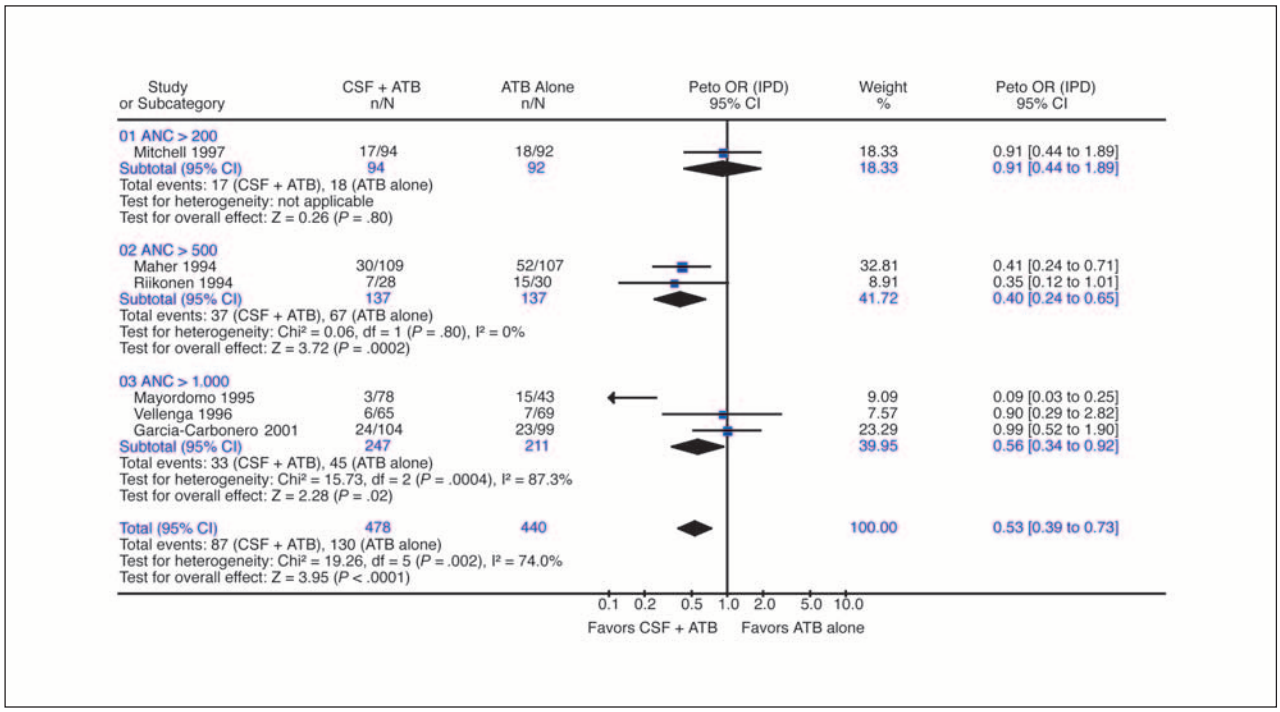

Fig 11. Colony-stimulating factors (CSF) for the treatment of chemotherapy-induced febrile neutropenia. Comparison: influence of the criteria of hospital discharge on the possible effects of CSF. Outcome: absolute neutrophil count (ANC). OR, odds ratio; ATB, antibiotics; IPD, individual patient data.

meta-analysis is underpowered to observe an impact of the CSFs on these outcomes with any confidence. In subgroup analysis, patients with hematologic malignancies may benefit in terms of reduced mortality from this intervention, although the results are highly influenced by one trial[60] that showed a stronger effect of CSF. Given the fact that the effect of CSF on mortality has been greatly influenced by this trial[60] and that, if this study is excluded from analysis, the effect is no longer significant, we recommend caution in interpretation of these results.

In the meta-analysis presented here, a significant effect of CSF on length of hospitalization was detected and persisted when a number of further subgroup and sensitivity analyses were performed. Most importantly, the results remain significant when the meta-analysis is restricted to trials with adequate allocation concealment and to double-blind trials. This effect is also consistent across different criteria used to assess a patient's fitness for discharge from hospital. The observed benefit of CSFs in shortening the length of hospitalization has the potential to change current clinical practice. Shortening hospitalization means less cost, but this has to be weighed against the cost of CSF, and an economic analysis is needed to further study the impact of this effect. This shorter length in the hospital can also represent a better quality of life for patients,[67] but we did not perform a formal analysis of quality of life.

The effect of CSF on time to neutrophil recovery was already expected, but this is the first time that this faster recovery is linked to a clinical benefit, translated by a shorter length of hospitalization. There was insufficient data from the trials included in this analysis to further evaluate the time to resolution of fever and antibiotic withdrawal. This late end point also has the potential to influence decisions about the use of CSF because the antibiotics used are usually expensive and can represent a substantial cost. The median time to antibiotic withdrawal was 1 day shorter in all trials.

Reported side effects of CSF use, such as bone pain, joint pain, and flu-like syndromes, were common and, in some reports, intense but were not life threatening. These side effects were reported more commonly in the GM-CSF group. A recently published systematic review[68] addressed the question of the addition of CSF to antibiotics in the treatment of FN. This systematic review located 11 trials and performed a meta-analysis of the mortality that included nine trials. The relative risk for mortality was 0.71 (95% CI, 0.44 to 1.15), which is quite similar to that found in this present review. However, that study had a restrictive search strategy by including only articles in English published up to 1998 and did not search relevant meeting abstracts. As a result of these restrictions on the search, their review failed to identify and consider three studies that are included in the present analysis.[44,62,63] In addition, they failed to extract mortality data from two studies.[11,61] Although the results for mortality are similar to ours, the estimates provided here are more precise and reliable and permit several subgroup analyses according to methodologic characteristics.

In conclusion, the use of CSF treatment in patients hospitalized for established FN caused by cancer chemotherapy does not significantly change overall mortality but clearly reduces the time spent in the hospital and time to neutrophil recovery. A possible effect on infection-related mortality requires further investigation. However, given the significant findings reported here, it may be difficult to include a no treatment control arm in future studies except in low-risk patients. An individual patient data meta-analysis, if feasible, may help to further define the impact of the CSFs on infection-related mortality in hospitalized patients with FN.

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Authors' Disclosures of Potential Conflicts of Interest

The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Honoraria: Gary H. Lyman, Amgen. Research Funding: Gary H. Lyman, Amgen. For a detailed description of these categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the "Disclosure of Potential Conflicts of Interest" section of Information for Contributors found in the front of every issue.

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