Recombinant human erythropoiesis-stimulating agents and mortality in patients with cancer: a meta-analysis of randomised trials

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Summary

Background Erythropoiesis-stimulating agents reduce anaemia in patients with cancer and could improve their quality of life, but these drugs might increase mortality. We therefore did a meta-analysis of randomised controlled trials in which these drugs plus red blood cell transfusions were compared with transfusion alone for prophylaxis or treatment of anaemia in patients with cancer.

Methods Data for patients treated with epoetin alfa, epoetin beta, or darbepoetin alfa were obtained and analysed by independent statisticians using fixed-effects and random-effects meta-analysis. Analyses were by intention to treat. Primary endpoints were mortality during the active study period and overall survival during the longest available follow-up, irrespective of anticancer treatment, and in patients given chemotherapy. Tests for interactions were used to identify differences in effects of erythropoiesis-stimulating agents on mortality across prespecified subgroups.

Findings Data from a total of 13 933 patients with cancer in 53 trials were analysed. 1530 patients died during the active study period and 4993 overall. Erythropoiesis-stimulating agents increased mortality during the active study period (combined hazard ratio [cHR] 1·17, 95% CI 1·06–1·30) and worsened overall survival (1·06, 1·00–1·12), with little heterogeneity between trials (I^2 0%, p=0·87 for mortality during the active study period, and I^2 7·1%, p=0·33 for overall survival). 10 441 patients on chemotherapy were enrolled in 38 trials. The cHR for mortality during the active study period was 1·10 (0·98–1·24), and 1·04 (0·97–1·11) for overall survival. There was little evidence for a difference between trials of patients given different anticancer treatments (p for interaction=0·42).

Interpretation Treatment with erythropoiesis-stimulating agents in patients with cancer increased mortality during active study periods and worsened overall survival. The increased risk of death associated with treatment with these drugs should be balanced against their benefits.

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Introduction

Erythropoiesis-stimulating agents increase haemoglobin concentrations, reduce the need for red blood cell transfusions, and could improve quality of life in patients with cancer.[1–3] However, they have been reported to increase the risk of thromboembolic events[2,4] and might stimulate tumour growth.[5] Uncertainty remains about whether and how these drugs affect survival; their safety has been discussed repeatedly at hearings of the US Food and Drug Administration and the European Medicines Agency.[4,6–12]

Previous studies addressing this issue were literature-based meta-analyses of aggregated results that combined heterogeneous mortality endpoints and could not examine whether effects differed across subgroups—eg, patients with different haemoglobin concentrations at baseline.[2–4] These limitations can be overcome in meta-analyses that are based on individual patient data, but up till now such meta-analyses have been small (2301[13] and 2112[14] patients), focused on epoetin beta or darbepoetin alfa, and were sponsored by the manufacturers.[13,14] Since erythropoiesis-stimulating drugs are widely used in patients with cancer, more definitive analyses of mortality in individuals randomly assigned to receive or not to receive these drugs are needed.

We therefore did a comprehensive meta-analysis that was based on the individual patient data from randomised controlled trials, including trials done by manufacturers of erythropoiesis-stimulating agents and independent investigators. Our objectives were to examine the effects of these drugs on the survival of patients with cancer and to identify factors that might modify such effects.

Methods

Patients and study selection

Main analyses were defined in a peer-reviewed protocol[15] and a statistical analysis plan, and main analyses were done independently in two academic departments. A steering committee consisting of clinicians and methodologists reviewed results and agreed on their interpretation.

In eligible studies, epoetin or darbepoetin plus red blood cell transfusions (as necessary) were compared with red blood cell transfusions (as necessary) alone to prevent or treat anaemia in adult or paediatric patients with cancer with or without concurrent antineoplastic treatment. Trials with high-dose, myeloablative chemotherapy regimens followed by stem cell transplantation were excluded, and those in patients with myelodysplastic syndromes, acute leukaemia, or those using erythropoiesis-stimulating agents for short-term preoperative treatment. Trials or trial strata were excluded if more than 20% of patients had an ineligible condition. Studies with planned sample sizes fewer than 100 patients or analyses based on fewer than 50 patients were also excluded.

We searched Medline, Embase, Cochrane Library, and conference proceedings, from Jan 1, 1985, to Jan 31, 2008, for eligible trials (for the detailed search strategy see Bohlius and colleagues[15]). Searches were supplemented with studies identified by manufacturers of erythropoiesis-stimulating agents. Two reviewers (JB, OW) independently assessed studies for eligibility, and discrepancies were resolved by consensus.

Manufacturers and triallists provided individual patient data and study variables in a standardised format. All data were anonymised, encrypted, and sent to the data centre at the University of Cologne, Cologne, Germany, where data were checked for accuracy, consistency, plausibility, and completeness of follow-up. Two reviewers (JB, SK) independently extracted additional study data from reports, study protocols, and clinical study reports.

Outcomes, definitions, and study quality

The primary outcomes were mortality during the active study period and overall survival in all patients and in those on chemotherapy. We defined mortality during the active study period as death from any cause between date of randomisation and 28 days after the end of the active study phase, and overall survival as death from any cause between date of randomisation and date of the last available follow-up. We classified studies according to cancer treatments (chemotherapy, radiotherapy, radiochemotherapy, no treatment, or other). At least 70% of patients had to be given the planned anticancer treatment to qualify for a particular category. The quality of studies was assessed independently by JB and SK using study protocols, clinical study reports, publications, and additional information from investigators. The components examined included generation of randomisation sequence (adequate *vs* unclear), concealment of allocation (adequate *vs* unclear), blinding (double-blind, placebo-controlled *vs* other), type of mortality endpoint (primary *vs* secondary endpoint *vs* adverse event), planned long-term follow-up (yes *vs* no), use of standardised chemotherapy or radiotherapy treatment protocol (yes *vs* no), and termination of study earlier than planned (yes *vs* no).

Statistical analysis

For each trial, we examined differences in baseline characteristics and follow-up times between patients given erythropoiesis-stimulating agents and those in the control groups, and assessed the proportional hazard assumption. Both one-stage and two-stage meta-analytic methods were used to analyse individual patient data.[16] We calculated log hazard ratios with log-rank test and Cox regression for each study and combined these in fixed-effects and random-effects meta-analyses (two-stage method). We also calculated Cox regression models stratified by study (one-stage fixed-effects method). Trials with no events in both groups did not contribute to meta-analyses. All analyses were by intention to treat. In the two-stage method, between trial heterogeneity was assessed by the I^2 statistic, and funnel plot asymmetry was assessed with linear regression.[17,18] We assessed the effect of individual studies on combined estimates.

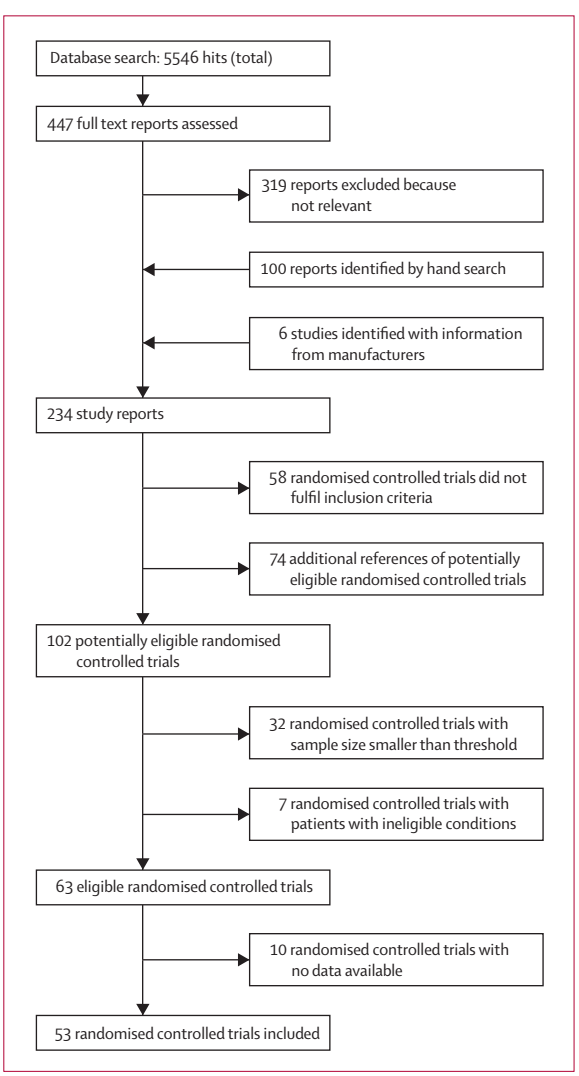

Figure 1: **Identification of eligible trials**

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	ESA	Control
Total	7634 (55%)	6299 (45%)
Haemoglobin concentration (g/L)		
≤80	448 (6%)	343 (5%)
>80 to ≤100	2222 (29%)	1708 (27%)
>100 to ≤120	2851 (37%)	2153 (34%)
>120 to ≤140	1433 (19%)	1410 (22%)
>140	428 (6%)	411 (7%)
Missing/not reported	252 (3%)	274 (4%)
Tumour type		
Haematological	1400 (18%)	1003 (16%)
Breast	2245 (29%)	2057 (33%)
Head and neck	443 (6%)	425 (7%)
Lung	1618 (21%)	1458 (23%)
Gastrointestinal	434 (6%)	274 (4%)
Gynaecological	842 (11%)	557 (9%)
Genitourinary	266 (3%)	176 (3%)
Other	369 (5%)	324 (5%)
Missing/not reported	17 (<1%)	25 (<1%)
Tumour stage		
Metastatic/advanced	4482 (59%)	3631 (58%)
Not metastatic or advanced	2116 (28%)	1923 (31%)
Unclear, missing, not reported	1036 (14%)	745 (12%)
Sex		
Men	2854 (37%)	2282 (36%)
Women	4780 (63%)	4017 (64%)
Age (years) at randomisation		
<18	55 (<1%)	68 (1%)
≥18 to <35	191 (3%)	155 (2%)
≥35 to <45	745 (10%)	598 (9%)
≥45 to <55	1614 (21%)	1396 (22%)
≥55 to <65	2237 (29%)	1956 (31%)
≥65 to <75	1970 (26%)	1547 (25%)
≥75	816 (11%)	573 (9%)
Missing/not reported	6 (<1%)	6 (<1%)
Haematocrit baseline categories		
≤0·235	210 (3%)	180 (3%)
>0·235 to ≤0·294	1567 (21%)	1221 (19%)
>0·294 to ≤0·353	2692 (35%)	1923 (31%)
>0·353 to ≤0·412	1258 (16%)	1200 (19%)
>0·412	414 (5%)	371 (6%)
Missing/not reported	1493 (20%)	1404 (22%)
Baseline serum erythropoietin (IU/L)		
<25	876 (11%)	621 (10%)
≥25 to <100	1643 (22%)	1265 (20%)
≥100 to <200	451 (6%)	289 (5%)
≥200 to <500	190 (2%)	135 (2%)
≥500	103 (1%)	78 (1%)
Missing/not reported	4371 (57%)	3911 (62%)
(Continues in next column)		

	ESA	Control
(Continued from previous column)		
Baseline ECOG performance status		
0, 1, or 2	5578 (73%)	4505 (72%)
3 or 4	79 (1%)	63 (1%)
Missing/not reported	1977 (26%)	1731 (27%)
Body-mass index (kg/m^2)		
<19	424 (6%)	441 (7%)
>19 to ≥25	2964 (39%)	2523 (40%)
>25 to ≥30	1864 (24%)	1579 (25%)
>30	867 (11%)	783 (12%)
Missing/not reported	1515 (20%)	973 (15%)
Recorded history of thromboembolic event		
Yes	318 (4%)	243 (4%)
No	5044 (66%)	4015 (64%)
Missing/not reported	2272 (30%)	2041 (32%)
Recorded history of cardiovascular event		
Yes	2002 (26%)	1591 (25%)
No	3700 (48%)	3029 (48%)
Missing/not reported	1932 (25%)	1679 (27%)
Recorded history of hypertension		
Yes	1219 (16%)	874 (14%)
No	4143 (54%)	3384 (54%)
Missing/not reported	2272 (30%)	2041 (32%)
Recorded history of diabetes mellitus		
Yes	372 (5%)	337 (5%)
No	3927 (51%)	3389 (54%)
Missing/not reported	3335 (44%)	2573 (41%)
Region		
Northern America	2004 (26%)	1565 (25%)
Northern, southern, western Europe	4030 (53%)	3410 (54%)
Eastern Europe	1030 (13%)	925 (15%)
Australia and New Zealand	216 (3%)	126 (2%)
Other	123 (2%)	103 (2%)
Missing/not reported	231 (3%)	170 (3%)
Chemotherapy given before study		
Yes	3111 (41%)	2262 (36%)
No	2558 (34%)	2301 (37%)
Missing/not reported	1965 (26%)	1736 (28%)
Radiotherapy given before study		
Yes	487 (6%)	390 (6%)
No	4618 (60%)	3693 (59%)
Missing/not reported	2529 (33%)	2216 (35%)

Data are number (%). ECOG=Eastern Cooperative Oncology Group. ESA= erythropoiesis-stimulating agents.

Table: **Patient characteristics at baseline**

We adjusted for baseline imbalances of prognostic factors in stratified Cox models (one-stage method). Patients were excluded from analyses if data for variables included in the model were missing. Variables with a p value from the likelihood-ratio test of less than 0·10 were included in multivariate models. Potential effect modifiers were examined in models that included an additional variable besides the treatment factor. Variables in these models were age; sex; baseline concentrations of

haemoglobin, haematocrit, and serum erythropoiesis-stimulating hormones; haemoglobin treatment upper limits; history of thromboembolism, cardiovascular events, diabetes, and arterial hypertension; type and stage of tumour; frequency of administration, duration of treatment, and dose of erythropoiesis-stimulating agents; and components of study quality. We also did posthoc analyses stratified by the Food and Drug Administration licensing indications (on-label *vs* off-label). In sensitivity analyses of placebo-controlled trials, we excluded patients who had not been given the intervention they were assigned to (per-protocol analysis) and estimated the complier-averaged causal effect on mortality during the active study periods.[19] Further details on these sensitivity analyses are provided in the webappendix (p 49).

Results are presented as hazard ratios (HRs) with 95% CIs for comparison of a erythropoiesis-stimulating agent with the control. We calculated numbers needed to treat for an additional death (NNTH).[20] Main statistical analyses were done independently at the Institute of Social and Preventive Medicine at the University of Bern, Switzerland, and the Institute of Medical Biometry and Medical Informatics at the University of Freiburg, Germany. Analyses were done in Stata (version 10.1) and R (version 2.7.1).[21]

Role of the funding source

Representatives of the manufacturers of erythropoiesis-stimulating agents contributed data and were members of the advisory board. Manufacturers and funding sources had no influence on the study design, analysis, and interpretation of data, writing of the report, and decision to submit the report for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 63 eligible studies and 53 (84%) contributed individual patient data (figure 1). Three manufacturers of erythropoiesis-stimulating agents (Amgen, Johnson & Johnson, and Hoffmann-La Roche) and five independent investigators provided individual patient data.[9,22–25] 14 206 patients were included in the dataset; 273 (2%) were excluded for the following reasons: no study arm was allocated (n=164), they had leukaemia and were included in a separate stratum (n=98),[26] or date of randomisation was missing (n=11). A total of 13 933 patients were included in the analyses (further details are provided in the webappendix p 1).

Chemotherapy was given to patients in 38 (72%) of 53 studies included in the meta-analysis (Angermund R and Murphy R, Janssen-Cilag, personal communication),[11,22,23,25–57] radiotherapy in three (6%),[6,24,58] and radiochemotherapy in five (9%).[9,59–62] In a further five (9%) studies, no chemotherapy or radiotherapy was given to patients.[10,63–66] Two studies were assessed in the category

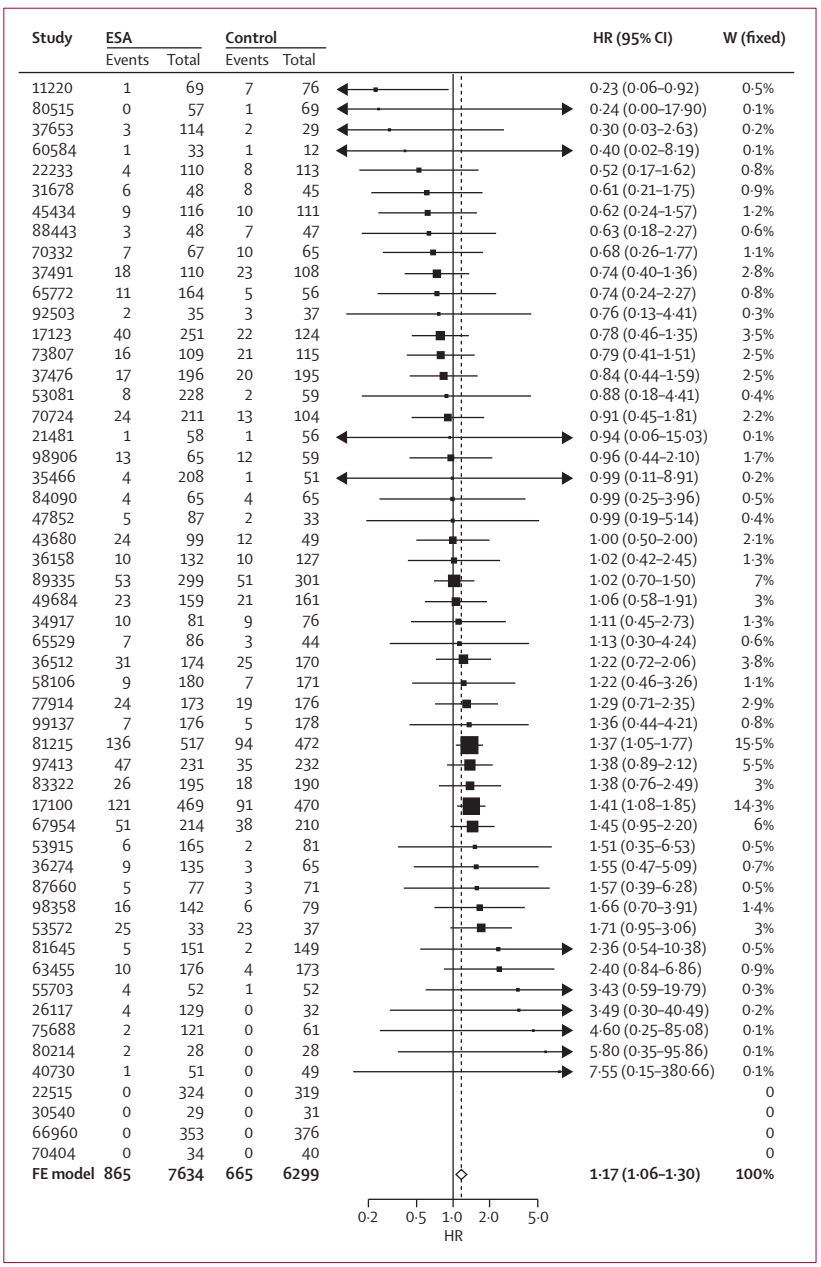

Figure 2: **Mortality in all patients with cancer during active study periods**
Each solid square represents a hazard ratio (HR) for individual trials, and the size of the square represents the weight of the individual study in the meta-analysis. Horizontal lines indicate 95% CIs. The width of the diamond shows the 95% CI for the pooled HRs. ESA=erythropoiesis-stimulating agents. FE=fixed-effects. W (fixed)=weight based on fixed-effects models.

called other since less than 70% of patients included had been given chemotherapy.[67,68] 28 (53%) studies were placebo-controlled. Randomisation procedures were adequately reported in 16 (30%) studies, and the method of randomisation was unclear in the remaining 37 (70%). Survival was the primary endpoint in five (9%) studies[23,29,32,37,61] and the secondary endpoint in 15 (28%) studies, and mortality was included as a safety or adverse outcome in 33 (62%) studies. Two (4%) studies were in

See Online for webappendix

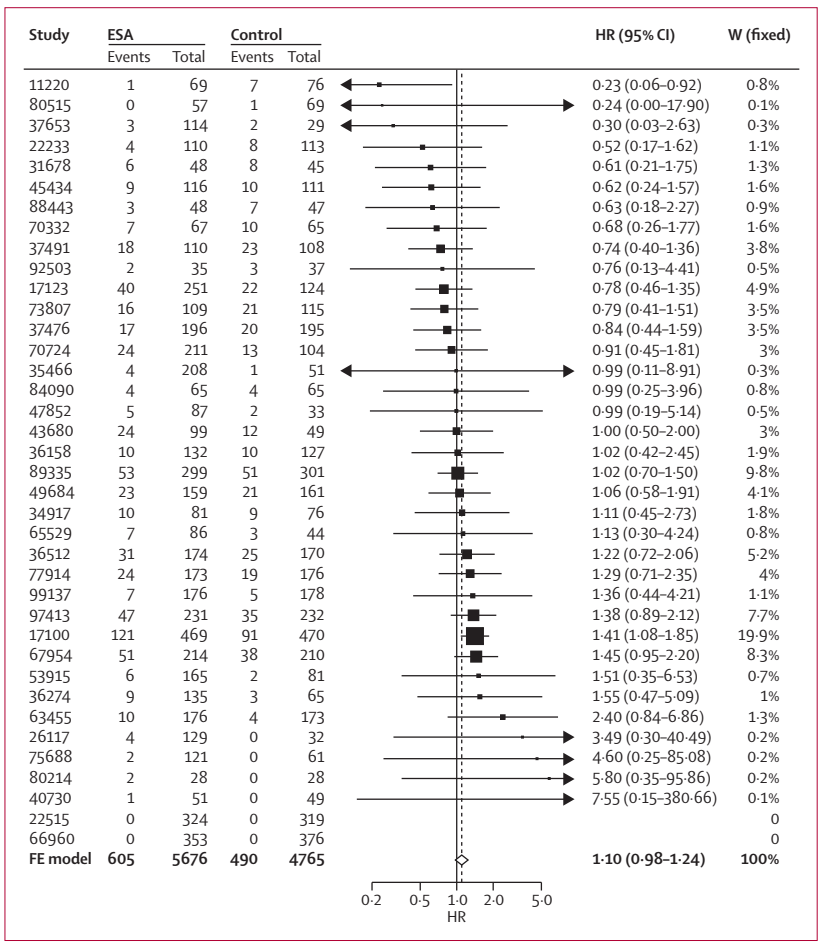

Figure 3: **Mortality in chemotherapy trials during active study periods**
Each solid square represents the hazard ratio (HR) of individual trials, and the size of square represents the weight of the individual trial in the meta-analysis. Horizontal lines indicate 95% CIs. The width of the diamond shows the 95% CI for the pooled HRs. ESA=erythropoiesis-stimulating agents. FE=fixed-effects. W (fixed)=weight based on fixed-effects models.

progress at the time of analysis, 14 (26%) ended prematurely, and 37 (70%) were completed.[22,23]

The planned epoetin dose was from 21000 IU to 63000 IU per week, and that for darbepoetin was from 100·0 μg to 157·5 μg per week. The planned duration of treatment with erythropoiesis-stimulating agents was from 8 weeks to 52 weeks; in 20 (38%) studies the duration depended on the duration of chemotherapy. The median haemoglobin concentration achieved during the first 4 months of the active study period in patients given erythropoiesis-stimulating agents was equal to or greater than 150 g/L in two studies[6,58] and equal to or greater than 140 g/L in four studies.[23,24,50,62] In the other studies, which included 12245 (88%) of 13933 individuals in the total study population, the median achieved concentration of haemoglobin was less than 140 g/L (IQR 103–121; further details are provided in the webappendix p 3).

The table shows the baseline characteristics of the patients. The imbalance in the proportion of patients randomly assigned to the treatment and control groups is explained by the inclusion of trials with 2:1 randomisation and trials including more than one arm of erythropoiesis-stimulating agents. Median age at randomisation was 60·6 years (IQR 51·5–69·2) for patients treated with erythropoiesis-stimulating agents and 59·8 years (50·8–68·1) for those in the control groups. Median haemoglobin concentration at baseline was 106 g/L (96–121) in patients treated with erythropoiesis-stimulating agents and 108 g/L (96–125) in those in the control groups. The most frequent tumours were breast cancer (4302 [31%] of 13933) and lung cancer (3076 [22%]).

In the assessment of mortality during the active study period, median follow-up of all patients assigned to treatment with erythropoiesis-stimulating agents was 3·7 months (IQR 2·8–5·1) and 3·9 months (2·9–5·3) for those in the control groups. The combined HR was 1·17 (95% CI 1·06–1·30; p=0·003; figure 2). Trial results were homogeneous (I^2 0%, p=0·87) and the results with fixed-effects and random-effects models were identical. Two studies[7,66] contributed more than 10% weight to the overall analysis. Results were robust when we excluded one study at a time. In 38 chemotherapy trials, 5676 patients were randomly assigned to erythropoiesis-stimulating agents and 4765 to control. Median follow-up of patients in chemotherapy trials was 4·1 months (IQR 3·0–5·6) in the erythropoiesis-stimulating agent groups and 4·3 months (3·4–5·7) in the control groups. The combined HR was 1·10 (95% CI 0·98–1·24; p=0·12; figure 3), with little evidence of heterogeneity between trials (I^2 0%, p=0·72). One study[7] contributed 20% weight to the overall analysis; exclusion of this study reduced the overall HR to 1·03 (0·90–1·18); and exclusion of other studies did not substantially affect the results. Similarly, results changed little when we excluded patients who had not been given chemotherapy in trials classified as chemotherapy trials.

In the assessment of overall patient survival, median follow-up of all patients was 6·2 months (IQR 3·2–15·4) in the erythropoiesis-stimulating agent arm and 8·3 months (3·7–19·6) in the control arm. The combined HR was 1·06 (95% CI 1·00–1·12; p=0·046, n=13933), with little evidence of heterogeneity (I^2 7·1%, p=0·33). Two studies[29,64] contributed about 10% weight to the overall analysis. Exclusion of these had little effect on the overall result. In the 38 chemotherapy trials, median follow-up was 6·7 months (IQR 3·4–15·7) in the erythropoiesis-stimulating agent arm and 8·4 months (3·7–19·1) in the control arm. The combined HR was 1·04 (95% CI 0·97–1·11; p=0·263, n=10441), with little evidence of heterogeneity between trials (I^2 5·3%, p=0·38). Two studies[29,32] contributed about 10% weight to the overall analysis. Exclusion of any individual study did not greatly change the combined estimate.

Results for mortality during the active study period for all patients with cancer were stratified by study characteristics (figure 4) and patient characteristics

(figure 5). Most variables showed little evidence of effect modification, which was also the case when we compared trials in patients given different anticancer treatments (figure 4). The increase in mortality seemed to be more pronounced in patients treated with erythropoiesis-stimulating agents once per week than in those who were treated with these drugs more or less often (figure 4); however, differences were attenuated when we adjusted for other characteristics (planned dose of erythropoiesis-stimulating agent, endpoint of study, calendar year of last patient randomised). There was some evidence to suggest a substantial effect in patients with low baseline haematocrits (figure 5). Conversely, these drugs did not seem to increase mortality in patients with a history of thromboembolic events (figure 5). Effects tended to be pronounced in trials of high quality (ie, placebo-controlled, designed for overall survival, adequate reporting of concealment of allocation) but formal tests of interaction were not significant (p>0·20). There was little evidence for a difference in effects on mortality during the active study period whether or not erythropoiesis-stimulating agents were given according to Food and Drug Administration licensing indications for November, 2007, and July, 2008 (p from test of interaction >0·30; webappendix pp 44–45). Of note, erythropoiesis-stimulating agents were not administered exactly according to these indications in any of the trials. Results from stratified analyses for overall survival were similar (webappendix pp 28–41).

Results were similar in the sensitivity analyses when we used different statistical models or adjusted for baseline imbalances of prognostic factors (webappendix pp 42–43). Results did not change much when we included available results from the ten studies[8,69–77] for which individual patient data had not been available. There was little evidence of funnel plot asymmetry (p>0·10 from regression tests). For the active study periods, the results from per-protocol analyses of placebo-controlled trials and the estimate of complier-averaged causal effect were similar to those from the intention-to-treat analyses (webappendix pp 49–50).

We applied the overall estimate for mortality during the active study periods (HR 1·17, 95% CI 1·06–1·30) to different hypothetical patient populations with cancer. With an underlying survival probability of 95% at 1 year, the NNTH is 121 (69–343). With an underlying survival probability of 80%, the NNTH is 34 (19–94), and 24 (14–67) for a survival probability of 70%.

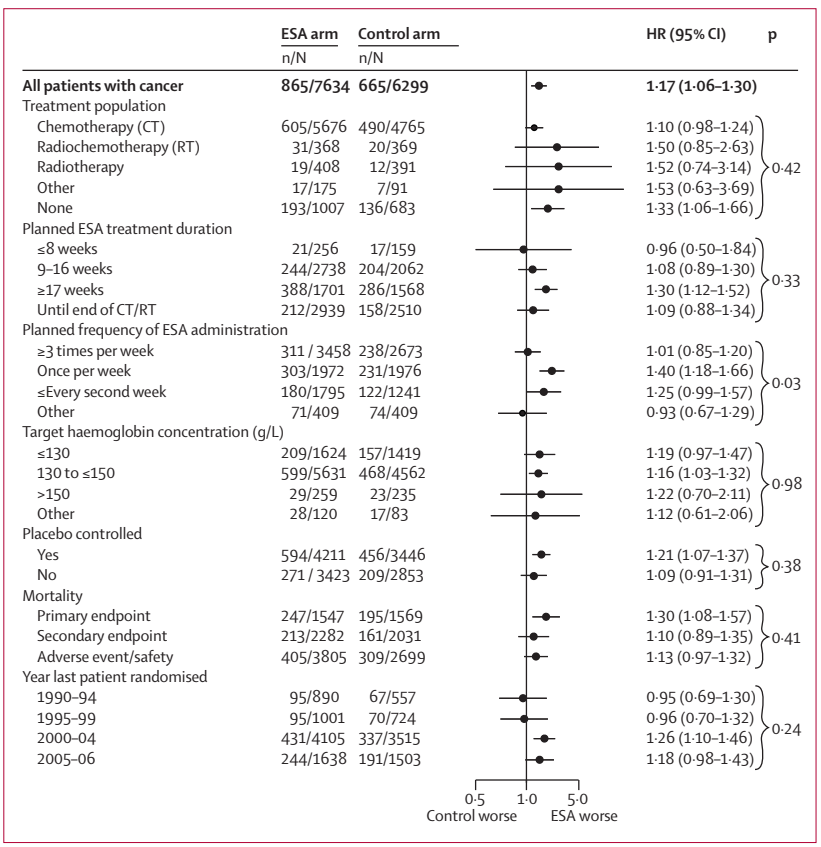

Figure 4: **Mortality in all patients with cancer during active study periods, stratified by study characteristics**
Solid circles represent subgroup hazard ratios (HRs). Horizontal lines indicate 95% CIs. The p value for interaction is based on fixed-effects Cox model stratified by study. ESA=erythropoiesis-stimulating agents. n=number of deaths. N=number of patients.

Discussion

Erythropoiesis-stimulating agents caused an estimated 17% increase in mortality relative to control during the active study periods in all patients with cancer and a 10% increase in relation to control in those undergoing chemotherapy. There was little evidence for differences in effects across different patient groups and trials. In particular, although mortality during the active study periods was less markedly increased in patients given chemotherapy than those given other treatments, this difference is compatible with random variation.

Our analysis has several strengths. It was based on individual patient data from 13 933 patients enrolled in randomised trials done by manufacturers and independent investigators. The main analyses were done in duplicate by two independent, experienced groups. Although the studies included clinically diverse populations and different treatment regimens of erythropoiesis-stimulating agents, there was little heterogeneity between results of different trials, and results were robust when subjected to various sensitivity analyses. Few modifiers of the effects of erythropoiesis-stimulating agents on mortality were identified. In view of the large dataset analysed, large differences were unlikely to be missed. However, we acknowledge that small differences cannot be excluded with certainty even in this study. Data were not available for some trials, particularly randomised controlled trials with radiotherapy or radiochemotherapy.[8,69,77] Inclusion of these studies with the published results did not, however, substantially change combined estimates. Only a few trials examined indications for erythropoiesis-stimulating agents that were similar to the approved

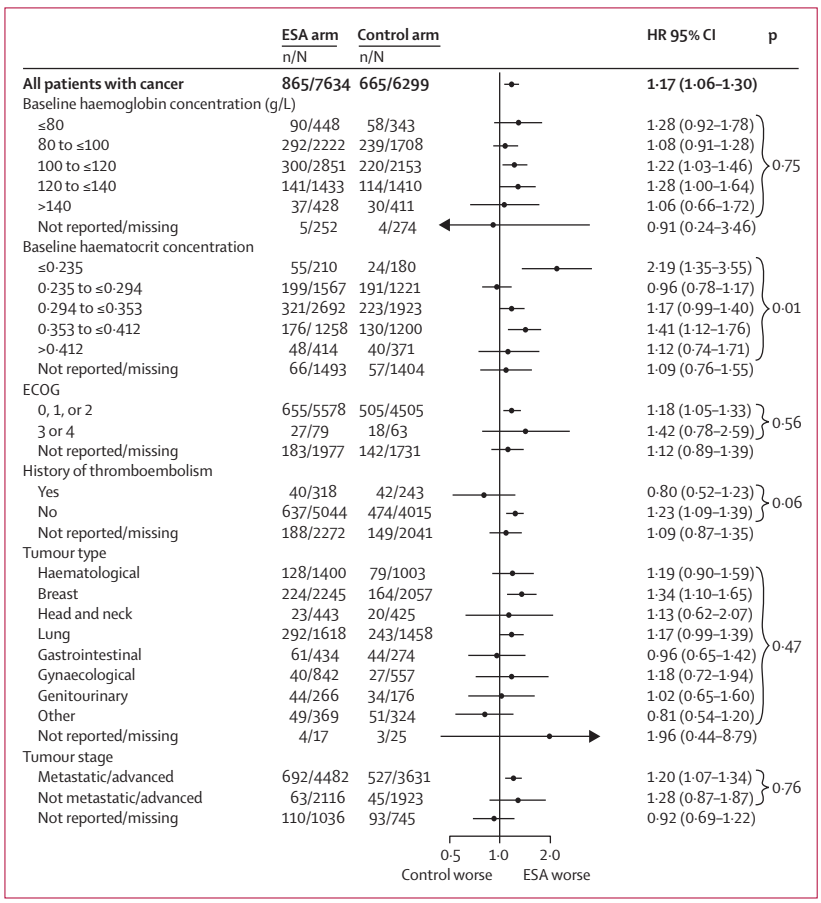

Figure 5: **Mortality in all patients with cancer during active study periods, stratified by patient characteristics**
Solid circles represent subgroup hazard ratios (HRs). Horizontal lines indicate 95% CIs. The p value for interaction is based on fixed-effects Cox model stratified by study. Subgroups of patients with unknown or missing values for a variable are shown but are excluded from the interaction test. ESA=erythropoiesis-stimulating agents. n=number of deaths. N=number of patients.

indications defined by the Food and Drug Administration, and our ability to detect differences between on-label and off-label use was therefore restricted.

By contrast with literature-based meta-analyses, which are restricted to aggregate data at study level, we could consider prognostic factors at the patient level in this meta-analysis of individual patient data. Subgroups of interest could be investigated and the modification of effects by patient and study characteristics examined in detail. Uniform survival endpoints could be defined and both mortality during the active study periods and overall survival based on the longest available follow-up analysed. Although the analysis of overall survival is important to examine long-term effects, results might be affected by confounding—eg, if control patients start treatment with erythropoiesis-stimulating agents after the end of the study. Also, progression of the underlying malignancy might dominate later on, and follow-up might be insufficiently rigorous, thus possibly diluting the effects of erythropoiesis-stimulating agents. We noted that increases in mortality associated with treatment with erythropoiesis-stimulating agents were more pronounced in analyses restricted to active study periods than the analyses of overall survival, which included additional follow-up. Previous literature-based meta-analyses[2,4,78] had to rely on reported results, with absent or inconsistent reporting of survival. Among the reports identified for 51 published studies we analysed, data for survival were not reported in five, data for mortality during the active study period were reported in 19, data for overall survival were reported in 14, and data for both endpoints were reported in 13. Previous meta-analyses[2,4,78] combined results for mortality during the active study periods with data for overall survival, which mitigated the noted increase in mortality associated with erythropoiesis-stimulating agents.

Some study authors argued that poor study designs could have introduced bias and, in particular, baseline imbalances favouring controls might at least to some extent explain the increased mortality with erythropoiesis-stimulating agents.[6,7,37,64] In this meta-analysis, effects tended to be increased in studies of good quality, and we found no evidence that baseline imbalances in prognostic factors affected results. High haemoglobin concentrations induced by erythropoiesis-stimulating agents, particularly when greater than 150 g/L, might impair tumour control or increase the risk of fatal thromboembolic and cardiovascular events.[6,79,80] Direct comparison of different target haemoglobin concentrations in patients with renal impairment showed increased mortality in patients treated to achieve high haemoglobin concentrations and those treated with high doses of erythropoiesis-stimulating agents.[81–83] We noted little evidence for an interaction between treatment with erythropoiesis-stimulating agents, haemoglobin concentration at baseline, target haemoglobin concentrations, planned doses of erythropoiesis-stimulating agents, and mortality. Patients with low haematocrits (<0·235) at baseline and being given erythropoiesis-stimulating agents had an increased risk of death compared with other subgroups: low haematocrits might be a marker for advanced cancer and increased vulnerability to the detrimental effects of erythropoiesis-stimulating drugs. Patients with increased frequency of treatments with erythropoiesis-stimulating agents had a reduced likelihood of death compared with others, yet no clear dose-response association was noted, and the association was confounded by other study characteristics.

Other explanations relate to effects of these drugs on the vascular system and tumour tissue. Increasing evidence suggests that erythropoiesis-stimulating agents might cause thromboembolic and cardiovascular events independently of haemoglobin concentrations.[84–87] In our analysis, patients with previous thromboembolic events being treated with erythropoiesis-stimulating agents seemed to be protected against an increase in mortality associated with these agents. Prophylactic anticoagulation during cancer treatment in patients with previous

thromboembolic events might have protected them against the thrombogenic effects of erythropoiesis-stimulating agents. A randomised trial in critically ill patients showed that those undergoing treatment with heparin did not have an increased risk of developing thromboembolic complications when treated with erythropoiesis-stimulating agents.[88] Of note, patients with a history of thromboembolic events were equally likely to receive the study drugs and the proportion of those with a history of thromboembolic events was well balanced between study arms. This finding might nevertheless be due to chance. Whether endogenous or exogenous erythropoietins stimulate proliferation of cancer cells expressing erythropoietin receptors is still undergoing debate.[89,90] However, epoetin-receptor status of tumours was not assessed in the trials included in our meta-analysis.

Whether erythropoiesis-stimulating agents are safer in patients undergoing chemotherapy than in those undergoing radiochemotherapy, radiotherapy, or no anticancer treatment is a matter of debate. These drugs increased mortality in patients undergoing chemotherapy by 10%. Statistically, the estimated mortality increase in chemotherapy trials is compatible with that in other trials (figure 4). Clinically, patients not given myelosuppressive anticancer treatment are more likely to achieve higher haemoglobin concentrations than those who are not, and might therefore be at increased risk of thromboembolic events and impaired tumour control. The difference between chemotherapy trials and those in patients given other anticancer treatments might thus be real, but have been missed even in this large collaborative study. The increase in mortality associated with erythropoiesis-stimulating agents might be less pronounced or even absent in cancer patients given chemotherapy than in those undergoing other anticancer treatments.

In conclusion, the findings of this individual patient data meta-analysis show that erythropoiesis-stimulating agents increase mortality in all patients with cancer, and a similar increase might exist in patients on chemotherapy. Most randomised trials and previous meta-analyses have shown that erythropoiesis-stimulating agents increase haemoglobin concentrations, reduce the need for transfusions,[1–3] and reduce fatigue.[91] In clinical practice, the increased risks of death and thromboembolic events[2,4] should be balanced against the benefits of treatment with erythropoiesis-stimulating agents, taking into account each patient's clinical circumstances and preferences. More data are needed for the effect of these drugs on quality of life and tumour progression, and meta-analyses similar to this one will address these questions. Further research is needed to clarify cellular and molecular mechanisms and pathways of the effects of erythropoiesis-stimulating agents on thrombogenesis and their potential effects on tumour growth.

Contributors

JB, ME, GS, and ST wrote the first draft of the study protocol. JB, CB, MC, BD, ME, MF, AE, MP, DR, MS, GS, JS, DS, ST, OW, and MZ contributed to the final version. JB and OW did literature searches and selected studies. JB and SK extracted additional data. CB, MZ, and JB did the data management, and KS, GS, CB, ST, JB, and MZ did the statistical analyses. IR-C, MM, VM, GT, and MU contributed the data from trials they did. JB, ME, GS, ST, AE, JS, and MP wrote the first draft of the report, and all authors contributed to the final version. ME and AE supervised the study.
Steering committee: Julia Bohlius, Michael Clarke, Matthias Egger, Andreas Engert, Maryann Napoli, Margaret Piper, Dirk Rades, Martin Schumacher, Jerome Seidenfeld, Mark Somerfield, David Steensma.
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Data management of original study data: Shamshad Ali (GOG-191 study), Sophie Dussart (ELYPSE-4 study), Alex Fleishman and the Biometrics and Data Management staff (Amgen), Viktor Nendel and the Biometrics and Data Management staff (Hoffmann-La Roche), Steven Sun and the Biometrics and Data Management staff (Johnson & Johnson).

Conflicts of interest

JB received honoraria and travel grants from Amgen. AE received research funding and honoraria from Amgen, Roche, and Johnson & Johnson. GT received research funding for the GOG-191 study by Johnson & Johnson. BD received research funding from OrthoBiotech and consulted for Amgen. MM received honoraria from OrthoBiotech. VM received research funding and honoraria from Amgen, Bristol-Myers Squibb, GlaxoSmithKline, Johnson & Johnson, Novartis, Pfizer, and Roche. MU received research funding for the PREPARE study from Amgen and Bristol-Myers Squibb. MP is employed by the Blue Cross and Blue Shield Association, the trade organisation for the independent US Blue Cross Blue Shield health insurance plans, but is not involved in the determination of coverage and reimbursement policy for individual plans. The other researchers declare that they have no conflicts of interest.

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