Table IV. Within-trial costs ($US, 2004–5 values) and clinical outcomes in the base-case analysis[a]

Costs and outcomes	Epoetin alfa (n = 175)	Darbepoetin alfa (n = 177)	Difference (95% CI)
Direct medical costs[b]			
Inpatient care	2 374 (5271)	1 520 (3866)	855 (−33, 1955)
Transfusions	112 (276)	201 (477)	−89 (−170, −14)
Radiation therapy	10 (92)	22 (126)	−12 (−37, 9)
Haematology and laboratory fees	335 (72)	331 (68)	4 (−10, 20)
Non-chemotherapy concomitant medications[c]	938 (798)	923 (741)	15 (−148, 179)
Chemotherapy			
Medication[c]	3 841 (4756)	3 807 (4337)	34 (−904, 929)
Physician fees	935 (933)	937 (895)	−2 (−188, 192)
Study medication[d]			
Medication[e]	5 781 (3214)	5 824 (2900)	−42 (−658, 593)
Physician fees	198 (90)	111 (48)	86 (71, 101)
Total direct medical costs	14 525 (9167)	13 676 (7138)	849 (−866, 2530)
Indirect costs			
Patient time	451 (192)	425 (170)	26 (−11, 66)
Total direct medical and indirect costs	**14 976 (9247)**	**14 101 (7220)**	**875 (−849, 2607)**
Response metrics[f]			
Haemoglobin response [% (n)]	50.3 (88)	43.0 (76)	7.4 (−2.4, 17.3)
Haematological response [% (n)]	47.4 (83)	35.0 (62)	12.4 (1.3, 22.6)
AUC for change in haemoglobin (g/dL)	12.2 (13.5)	7.9 (12.8)	4.3 (1.7, 6.9)
Haemoglobin level (g/dL)[g]			
Week 5	11.0 (0.8)	10.4 (0.8)	0.6 (0.3, 0.9)
Week 9	11.5 (1.3)	10.9 (1.4)	0.6 (0.2, 0.9)
Week 13	11.9 (1.3)	11.1 (1.6)	0.8 (0.4, 1.2)
Week 17	11.9 (1.3)	11.5 (1.5)	0.4 (−0.2, 0.9)
Patients with haemoglobin ≥11 g/dL by week 5 [% (n)]	62.9 (110)	48.6 (86)	14.3 (3.5, 24.6)
Patients with haemoglobin ≥11 g/dL by week 9 [% (n)]	77.1 (135)	66.7 (118)	10.5 (1.2, 20.0)
Days of follow-up with haemoglobin 11–13 g/dL (%) [mean (SD)]	44.7 (30.1)	35.8 (29.2)	8.9 (2.8, 14.8)

a All values are mean (SD) unless otherwise indicated.

b Expressed in $US, year 2004 values unless otherwise indicated.

c Costs of non-study medications are based on 95% of the 2004 average wholesale price.

d Expressed in $US, year 2005 values.

e Costs of study medications are based on 95% of the average wholesale price in March 2005 for epoetin alfa (Procrit®, Ortho Biotech Products, LP, Raritan, NJ, USA) and darbepoetin alfa (Aranesp®, Amgen Inc., Thousand Oaks, CA, USA).

f Response metrics are based on observed haemoglobin values. Haemoglobin response consisted of a ≥1 g/dL rise in haemoglobin by week 5. Haematological response consisted of a ≥2 g/dL rise in haemoglobin by week 9.

g At week 9, n = 153 for epoetin alfa and n = 156 for darbepoetin alfa. At week 13, n = 123 for epoetin alfa and n = 122 for darbepoetin alfa. At week 17, n = 100 for epoetin alfa and n = 100 for darbepoetin alfa.

AUC = area under the curve.

Table V. Sensitivity analysis: varying methods to assign costs to study medications and administration[a]

Cost assignment method	Epoetin alfa (n = 175)	Darbepoetin alfa (n = 177)	Difference (95% CI)
Wholesale acquisition cost method			
Study medications (100% of wholesale acquisition cost)	5070	5102	−33 (−573, 525)
Physician fees[b]	198	111	86 (71, 101)
Total	5268	5214	54 (−504, 625)
Wholesale acquisition cost method			
Study medications (85% of wholesale acquisition cost)	4309	4337	−28 (−487, 446)
Physician fees[b]	198	111	86 (71, 101)
Total	4507	4449	59 (−417, 546)
Wholesale acquisition cost method			
Study medications (70% of wholesale acquisition cost)	3549	3572	−23 (−401, 367)
Physician fees[b]	198	111	86 (71, 101)
Total	3747	3683	64 (−331, 466)
Federal Supply Schedule method			
Study medications (100% of Federal Supply Schedule)	2329	2820	−491 (−762, −211)
Physician fees[b]	198	111	86 (71, 101)
Total	2527	2932	−405 (−691, −111)
Reimbursement-based methods			
Hospital outpatient clinic			
Study medications	4713	4374	339 (−149, 842)
Physician fees	220	124	96 (79, 113)
Total	4933	4498	436 (−73, 951)
Community physician office			
Study medications	4419	4079	340 (−117, 811)
Physician fees	186	105	81 (66, 95)
Total	4605	4183	422 (−52, 902)

a Values are expressed as $US, year 2005 values unless otherwise indicated.

b Physician fees are based on weighted averages of Medicare Part A[25] and Medicare Part B[26] reimbursement rates: 65% community-based, 35% hospital outpatient-based.

tion and administration costs, the cost per haematological response would be $US2523 for epoetin alfa and $US3391 for darbepoetin alfa.[2]

Sensitivity Analyses

Results from the first set of sensitivity analyses, in which we varied the sources for cost assignment to study medications and their administration, are reported in table V. When the wholesale acquisition cost was used to assign costs to study medications, mean drug costs over the follow-up period were approximately equal in both study groups, whereas when the Federal Supply Schedule was used, mean drug costs were $US491 higher for patients receiving darbepoetin alfa. When a reimbursement perspective was taken, reimbursement for epoetin alfa and darbepoetin alfa was approximately $US300 greater for hospital outpatient clinics than for com-

2 First, the costs (from table IV) for study drugs and administration were added together for each treatment group ($US5781 + 98 = $US5979 for epoetin, and $US5824 + 111 = $US5935 for darbepoetin). Then these numbers were multiplied by 0.2 to represent the patient co-payment. Then the co-payment was divided by the proportion of patients experiencing a haematological response in each treatment group (1196/0.474 = $US2523 for epoetin, and 1187/0.350 = $US3391 for darbepoetin). From an incremental perspective, this would result in an estimate of approximately $US75 per additional patient experiencing a haematological response ($US1196 − 1187)/(0.474 − 0.350) = $US73.

munity-based clinics. Nevertheless, the difference in reimbursement between study medications remained the same in both settings, with mean reimbursement approximately $US340 higher for patients receiving epoetin alfa. Mean reimbursement for drug administration was approximately $US80–100 higher per patient over the follow-up period for patients receiving epoetin alfa when either Medicare Part A or Part B reimbursement fees were assigned.

In the second set of sensitivity analyses, in which we assumed that patients would incur an office visit only when receiving erythropoietic therapy, patient time costs for those receiving epoetin alfa were, on average, $216 higher than with darbepoetin alfa ($442 vs $226). Then, using the base-case estimates regarding the frequency of visits and assigning costs only to the time that patients spent at the clinic, patient time costs were estimated to be $5 higher among patients receiving epoetin alfa than among darbepoetin alfa recipients over the course of the trial ($80 vs $75).

We performed the third set of sensitivity analyses to evaluate the impact of using the last value carried forward to impute haemoglobin values for the 28-day period after a blood transfusion. For both treatment groups, application of this method decreased the proportions of patients achieving all response metrics, decreased mean haemoglobin levels across all time points, decreased the AUC for change in haemoglobin and decreased the mean percentage of days of follow-up when patients were within the therapeutic range (table VI). Nevertheless, clinical outcomes remained superior among patients in the epoetin alfa group.

In the *post hoc* sensitivity analyses, we applied a commonly used method to assign inpatient costs in economic evaluations, in which unit costs were applied to hospitalisation events without making adjustments for differences in length of stay. In this analysis, the difference in costs between treatment arms decreased from $US855 in the base-case analysis to $US295 ($US1649 for epoetin alfa, $US1354 for darbepoetin alfa; 95% CI for the difference −341, 985). Then, to examine the impact of outliers, when we removed the top 5% of longest hospitalisations, mean inpatient costs remained $US576 higher among patients receiving epoetin alfa, but the difference was not statistically significant ($US1837 for epoetin alfa, $US1261 for darbepoetin alfa, 95% CI for the difference −161, 1387). When we removed the top 10% of longest hospitalisations, inpatient costs were $US285 higher in the epoetin alfa group ($US1477 vs $US1192, 95% CI for the difference

Table VI. Sensitivity analysis: clinical outcomes when applying the last value carried forward to impute haemoglobin values for 28 days after a blood transfusion

Response metrics[a]	Epoetin alfa (n = 175)	Darbepoetin alfa (n = 177)	Difference (95% CI)
Haemoglobin response [% (n)]	44.6 (78)	33.9 (60)	10.7 (1.7, 20.6)
Haematological response [% (n)]	44.6 (78)	27.1 (48)	17.5 (8.0, 26.7)
AUC for change in haemoglobin (g/dL) [mean (SD)]	11.1 (13.5)	6.0 (13.8)	5.1 (2.4, 7.7)
Haemoglobin level (g/dL) [mean (SD)][b]			
week 5	10.9 (1.5)	10.4 (1.4)	0.5 (0.3, 0.9)
week 9	11.2 (1.5)	10.6 (1.7)	0.6 (0.3, 1.0)
week 13	11.4 (1.4)	10.8 (1.7)	0.6 (0.3, 1.0)
week 17	11.4 (1.5)	10.9 (1.8)	0.5 (0.2, 0.9)
Patients with haemoglobin ≥11 g/dL by week 5 [% (n)]	56.0 (98)	44.6 (79)	11.4 (0.4, 21.0)
Patients with haemoglobin ≥11 g/dL by week 9 [% (n)]	71.4 (125)	59.3 (105)	12.1 (1.3, 21.3)
Days of follow-up with haemoglobin 11–13 g/dL (%) [mean (SD)]	42.4 (30.8)	33.7 (30.5)	8.7 (2.2, 14.8)

a Response metrics are based on observed haemoglobin values. Haemoglobin response consisted of a ≥1 g/dL rise in haemoglobin by week 5. Haematological response consisted of a ≥2 g/dL rise in haemoglobin by week 9.

b At week 9, n = 153 for epoetin alfa and n = 156 for darbepoetin alfa. At week 13, n = 123 for epoetin alfa and n = 122 for darbepoetin alfa. At week 17, n = 100 for epoetin alfa and n = 100 for darbepoetin alfa.

AUC = area under the curve.

−361, 950). Finally, when we tested the impact of different assumptions regarding the recording of chemotherapy data, cost differences for chemotherapy drugs and their administration remained close to zero between treatment groups.

Discussion

To our knowledge, this work represents the first published economic evaluation using data from a head-to-head trial of two erythropoietic agents. Strengths of the analysis included the randomised study design, the use of a pre-specified plan to assign costs and the detail provided in this paper to maximise the methodological transparency of our analyses. Overall, the results revealed that total costs over a mean follow-up of 12 weeks were non-significantly higher by approximately $US900 among patients receiving epoetin alfa than patients receiving darbepoetin alfa, of which 98% of the cost difference was attributable to higher inpatient costs. On the clinical side, therapy with epoetin alfa administered once weekly was shown to provide superior haematological outcomes relative to darbepoetin alfa administered once every 2 weeks using administration guidelines required by the protocol. In addition, when considering all transfusion episodes recorded over the follow-up period, patients receiving epoetin alfa required significantly fewer units of red blood cells than patients receiving darbepoetin alfa, resulting in a significant cost saving of approximately $US90 per patient (table IV).

In the base-case analysis in which we applied the average wholesale price, costs for study medications were almost equal. However, costs for drug administration were about $US100 higher for epoetin alfa because the drug is administered on a weekly basis as opposed to a biweekly basis for darbepoetin alfa. However, it appears that epoetin alfa provides a cost advantage for healthcare providers who can acquire drugs at costs close to those paid by the US Government. When the Federal Supply Schedule was used for cost assignment, drug costs were approximately $US500 lower for epoetin alfa. However, from the perspective of an individual provider, our estimates of both mean costs and reimbursements are meaningful.

For providers who pay close to the average wholesale price for epoetin alfa or darbepoetin alfa, reimbursement does not appear to be adequate to cover the cost, because there is a $US1000–1400 shortfall for hospital-based clinics reimbursed under Medicare Part A and a $US1300–1700 shortfall for outpatient physician practices reimbursed under Medicare Part B. At the other extreme, for those who pay costs as low as the federal government, reimbursement levels are higher than drug costs, ranging from about $US1300–2400. Although these findings are compelling, two issues should be considered.

First, a very small proportion of providers pay drug costs that are similar to either the average wholesale price or the Federal Supply Schedule. However, we have also provided results using costs between the average wholesale price and the Federal Supply Schedule (table V), which are more representative of prices paid by most providers in the US. Second, although we applied national average Medicare reimbursement rates for drug administration, the fees paid by individual Medicare carriers in different regions of the country may vary somewhat.

Perspective is also important when interpreting the results regarding physician fees for drug administration and patient time costs. From a physician's perspective, total reimbursement for drug administration is higher for epoetin alfa because of the greater frequency of drug administration. However, while it may seem, from the patient's perspective, that the time costs are greater with epoetin alfa, the extent to which this is true is somewhat debatable. Under the protocol for this trial, patients in both treatment groups were required to return every week for laboratory tests (complete blood cell counts, including differential and platelet counts). Thus, it was not possible to measure the potential benefit of administration every 2 weeks with darbepoetin alfa, so we relied on data from outside the trial to assign patient time costs. Using data from a retrospective study on resource use in two large oncology practices, Beveridge et al.[18] found that, although darbe-

poetin alfa was administered every 2 weeks in 92% of the patients, blood counts were generally performed weekly. As a result, the mean number of office visits over a 4-week period was 4.0 among patients receiving epoetin alfa and 3.8 among patients receiving darbepoetin alfa, demonstrating that for patients undergoing chemotherapy, patient time costs are not likely to be substantially altered with biweekly versus weekly administration over the first month.

We acknowledge that the follow-up period in the study by Beveridge et al.[18] was limited. We did not identify any additional published manuscripts that compared the need for outpatient visits between drug regimens. However, two recently reported abstracts have revealed a similar number of visits for patients treated with epoetin alfa or darbepoetin alfa.[39,40] In the study by Harley et al.,[39] there was an average of 10.7 visits in the epoetin alfa group and 10.3 in the darbepoetin group over a mean of 56 days of treatment. In the study by Gosselin et al.,[40] there was an average of 7.7 visits in the epoetin alfa group and 7.5 in the darbepoetin alfa group over a mean of 58 days of treatment. These findings support our use of the Beveridge et al.[18] study and provide further evidence that patients with cancer frequently incur office visits for multiple reasons (e.g. chemotherapy administration, nausea and pain control) rather than an isolated injection of an erythropoietic agent. Future studies should evaluate the extent to which biweekly administration actually decreases the number of office visits incurred by patients receiving various chemotherapy regimens over a longer time horizon.

The magnitude of the difference in inpatient costs between treatment groups was unexpected, but appears to be a result of more patients experiencing relatively longer hospitalisations in the epoetin alfa group. In economic evaluations where analysts directly assign unit cost estimates to hospitalisation events, differences in the duration of hospital stays between treatment groups would not be accounted for in cost comparisons. However, with our prespecified cost assignment method that makes adjustments for differences in length of stay, inpatient costs in our study were reflective of longer hospitalisations in the epoetin alfa group. We examined the hospitalisation data in further detail to explore potential reasons as to why hospital costs were higher among patients receiving epoetin alfa, but we failed to identify any patterns. Of the 15 longest hospitalisations, 12 occurred in the epoetin alfa group and three occurred in the darbepoetin alfa group. Only two of these hospitalisations appeared to be potentially related to chemotherapy-induced anaemia or the study drug (symptomatic anaemia and deep venous thrombosis). The others included four cases of infection and single cases of febrile neutropenia, dehydration, muscle weakness, respiratory distress, spinal compression, kidney failure, metastatic gastric cancer, gastroparesis and rectal sigmoiditis.

Insufficient detail regarding the reason for hospitalisation not only made it difficult to explore reasons why the duration of hospitalisations may differ, but also made the task of cost assignment inexact. For example, in many cases, the information provided in the case report form for the primary and secondary discharge diagnoses was limited to descriptions such as 'colorectal cancer' or 'progressive disease'. We had limited information as to whether patients were undergoing surgical and/or diagnostic procedures, receiving chemotherapy or palliative care or experiencing complications of progressive disease such as spinal cord compression. Although we assigned DRG codes without knowledge of treatment-group assignment, we have likely overestimated inpatient costs in some cases and underestimated costs in others, possibly contributing to the differences in inpatient costs found in this trial. Finally, the location of service (skilled nursing facility, subacute unit, etc.) in the inpatient setting was not identified, and this could also contribute to differences in inpatient length of stay and costs.

An alternative explanation for the greater number of inpatient days in the epoetin alfa group is that fewer of the sickest patients in this group died, so they experienced more days at risk for hospitalisation. Among the 352 patients analysed, 23 (13.1%) patients receiving epoetin alfa died compared with 32 (18.1%) patients receiving darbepoetin alfa

($p = 0.20$, based on chi-square test). Although this difference was not statistically significant, one might ponder the potential influence on inpatient days had these additional darbepoetin alfa patients not died.

An additional factor that may have played a role in differences in resource use was the open-label design of the trial. Although it would have been useful to evaluate the data for evidence of systematic bias at the investigator level, there was an average of only seven patients enrolled at each study site. With such small samples per site, it would not be possible to evaluate whether differences between treatment arms was due to potential bias or simply due to chance.

The methodology employed in this economic evaluation to analyse the clinical outcomes was different from that commonly used to measure the efficacy of erythropoietic agents. For example, we relied on observed haemoglobin values, which included the effects of blood transfusions. When assessing haemoglobin response rates, this approach favours the therapy with more transfusions. Yet, transfusion is the outcome that treatment is intended to prevent. Thus, the clinical data presented for use in the economic analysis are not meant to substitute for the clinical results reported for the study.[17] However, for the purposes of this economic analysis, since we included the costs of transfusions when calculating costs, the effects of transfusions on raising haemoglobin were also included.

Although QALYs have been used in some economic evaluations of erythropoietic therapies in cancer-related anaemia,[41-43] we concluded prior to conducting this analysis that this metric could not be appropriately estimated using data from this clinical trial. First, utility data were not collected from patients enrolled in the trial. We also reviewed the medical literature for information on the relationship between haemoglobin levels and utilities but failed to identify reliable evidence. For example, in a study of haemodialysis patients, scores from the Health Utilities Index did not differ between groups who were randomly assigned doses of epoetin alfa to attain haemoglobin levels of 10 g/dL or 13.5 g/dL.[44] Also, in one cost-effectiveness evaluation that attempted to measure QALYs, the calculations were not based on standard utility estimates but on data from the Linear Analog Scale Assessment.[41] Furthermore, most previous studies that estimated the cost per QALY were based on models that involved more general health states to which utility weights could be assigned, such as blood-borne diseases[41] and advanced cancer,[42] not health states defined by varying levels of haemoglobin.

Given the considerations discussed above, we feel justified in not carrying out a formal cost-utility analysis. However, we recognise that limiting the analysis to separate estimation of cost and outcomes limits the usefulness of the analysis for making resource allocation decisions across therapeutic areas. Nevertheless, this analysis was not designed to answer the question of whether to use erythropoietic agents, but rather to compare costs and clinical outcomes between the drugs. Therefore, for decision makers who are grappling with this question, we believe the objectively reported information reported here is meaningful.

Conclusion

Once-weekly administration of epoetin alfa largely demonstrated improved haematological outcomes compared with biweekly administration of darbepoetin alfa, but costs for study medications and most medical resources were similar. Given treatment guidelines for chemotherapy-induced anaemia, costs paid for erythropoietic agents relative to reimbursement levels reveal the potential for financial inequities across healthcare providers that could affect patients' access to these therapies.

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Clinical Benefits and Risks Associated with Epoetin and Darbepoetin in Patients with Chemotherapy-Induced Anemia: A Systematic Review of the Literature

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ABSTRACT

Background: Erythropoiesis-stimulating proteins (ESPs) are indicated for the treatment of chemotherapy-induced anemia (CIA). Evidence-based guidelines and systematic reviews of the management of CIA do not yet include all currently approved ESPs or all of the clinically relevant benefits and risks of ESPs.

Objectives: The aims of this work were to provide up-to-date assessments of biochemical (efficacy) and effectiveness (ie, transfusions and quality-of-life [QoL] benefits) and safety (ie, risk of venous thromboembolism [VTE] and all-cause or treatment-associated death) of epoetin-alfa, epoetin-β, and darbepoetin-alfa for the treatment of CIA in cancer patients with hemoglobin <11 g/dL. We also considered the impact of differences in study design, patients, and treatments on the results.

Methods: A systematic review of the literature was performed to identify and analyze English-language studies (controlled trials and prospective uncontrolled studies with ≥300 patients) published between 1980 and July 2005. The databases searched were MEDLINE and the Cochrane Library. Relevant abstracts from the last 2 annual meetings of the American Society of Clinical Oncology, American Society of Hematology, and European Society for Medical Oncology were also included. Studies were selected, using predefined eligibility criteria. Two reviewers had to agree on all included and excluded studies, and on all data extracted from each accepted study before they were entered into a relational database. Meta-analyses were performed to quantify benefit and risk outcomes.

Results: In total, 40 studies including 21,378 patients were eligible for analysis. Each ESP was found to have efficacy relative to standard care or placebo. The odds ratio (OR) for transfusions in studies of epoetin versus controls was 0.44 (95% CI, 0.35–0.55) and for darbepoetin versus controls was 0.41 (95% CI, 0.31–0.54). Patients receiving ESPs experienced a significant improvement in QoL; the mean difference in Functional Assessment of Cancer Therapy–Fatigue scores for ESPs versus controls was 0.23 (95% CI, 0.10–0.36; $P = 0.001$). The frequency of VTE and death was not significantly different between ESPs and control (VTE OR, 1.41 [95% CI, 0.81–2.47]; all-cause mortality OR, 1.00 [95% CI, 0.69–1.44]).

Conclusions: This analysis of key clinical benefits and risks of epoetin and darbepoetin in the treatment of CIA found no clinically relevant differences between these drugs. (*Clin Ther.* 2006;28:online) Copyright © 2006 Excerpta Medica, Inc.

Key words: anemia, darbepoetin-alfa, epoetin-alfa, epoetin-β, meta-analysis, systematic review, cancer.

INTRODUCTION

For patients with chemotherapy-induced anemia (CIA), evidence-based guidelines recommend maintaining hemoglobin (Hb) levels between 11 and 13 g/dL by treating with erythropoiesis-stimulating proteins (ESPs).[1–3] There are 3 ESPs currently marketed worldwide—epoetin-alfa, epoetin-β, and darbepoetin-alfa—but only epoetin-alfa and darbepoetin-alfa are available in the United States. Treatment guidelines from the American Society of Clinical Oncology (ASCO) and European Organization for Research and Treatment of Cancer do not address darbepoetin.[1,2] A recent sys-

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tematic review on the subject did not include studies published after 2001.[4] Although that review found epoetin to be efficacious in terms of clinically relevant outcomes (eg, transfusions), it did not address darbepoetin-alfa, nor did it quantify quality-of-life (QoL) measures. In addition, a Canadian technology assessment report was released in 2003 and updated in 2005,[5] but this also did not appear to include darbepoetin. Since then, published research has evaluated the efficacy, safety, and, to a lesser extent, effectiveness of all 3 ESPs. In addition, the product labels were recently changed[6] to address concerns about ESP-related risk of venous thromboembolism (VTE).

Therefore, we undertook a systematic review of the literature, including recent meeting abstracts, to provide up-to-date assessments of the clinical efficacy and effectiveness (transfusions and QoL benefits) and safety (risk of VTE and all-cause or treatment-associated death) of epoetin-alfa, epoetin-β, and darbepoetin-alfa for the treatment of CIA in cancer patients with anemia (ie, Hb <11 g/dL). We also considered the impact of differences in study design, patients, and treatments on the results.

METHODS

Literature Search

Systematic review methods[7,8] were used to identify and analyze English-language studies published as full papers between 1980 and July 2005, or as abstracts from the 2003, 2004, or 2005 annual meetings of ASCO, American Society of Hematology, or European Society of Medical Oncology. (Studies published as abstracts >2 years earlier were assumed to have been published subsequently as full papers.) MEDLINE (via PubMed) was searched for citations using the following search strategies: first, *erythropoietin* or *epoetin* or *EPO* or *Procrit* or *Epogen* or *darbepoetin* or *DARB* or *ARANESP* or *NESP*; second, *neoplasms* [MeSH] or *cancer* or *oncology* or *tumor* or *tumors* or *tumour* or *tumours* or *malignanc** ; and results of the first and second searches with limits on publication date (1999–2005), language (English), study type (clinical trial), and population (humans).

The literature was searched back to 1999 because this search was an update of a previous search and review we had performed of the same subject, in which the search interval began in 1980. In addition to MEDLINE, we used 2 strategies to identify recently published papers that may not yet be indexed on MEDLINE. First, we did a PubMed key word search for the past 6 months with no limits. Second, we did a Current Contents search for the past 6 months, using the same search terms. The search cutoff date was July 10, 2005.

The Cochrane Library was searched for any recent systematic review of the subject, which could then serve as a source of further references. The Cochrane search was performed using similar terms as for the 6-month key word and Current Contents searches already described. Finally, a manual check of the reference lists of all accepted papers and of recent reviews and meta-analyses was performed to supplement the electronic searches. We did not pursue manufacturers or study authors to identify other unpublished sources of information.

Study Eligibility

Both randomized and nonrandomized but controlled trials of patients (adults or children) treated for CIA (ie, baseline Hb <11 g/dL) were eligible for the review. We also included prospective, uncontrolled studies enrolling ≥300 CIA patients to permit an analysis of effectiveness and safety in real-world patient populations. Anemia treatment was defined as the use of an approved ESP (epoetin-alfa, epoetin-β, or darbepoetin-alfa) compared with the standard care (typically transfusions), placebo, or both, or compared with another ESP (if a controlled trial) or with no comparator group (if a community-based study). At least 10 patients per treatment group were required for studies to be included in the review, and an outcome of interest had to be extractable by anemia treatment group. The 10-patient threshold for acceptance is an arbitrary requirement we frequently use in our systematic reviews. The 300-patient threshold for overall sample size is also arbitrary, and was intended to permit inclusion of any potentially important and substantive community-based single-arm studies.

To examine the relationship between safety outcomes and baseline Hb, we included additional studies that enrolled patients with a higher baseline Hb. Aside from baseline Hb, these additional studies met all of the predefined eligibility criteria.

For all accepted studies, as well as those rejected for not satisfying all inclusion criteria, the agreement of 2 independent reviewers was required (Figure 1).

Database Development

Data elements describing study, patient and treatment characteristics, and outcomes of interest were ex-

tracted from each eligible study onto data-extraction forms developed for this project. Randomized controlled trials (RCTs) were scored for quality using the Jadad method,[9] whereby points are assigned for the description of the randomization and blinding procedures, and for accounting for all withdrawals. The range of possible scores is 0 to 5, with higher numbers indicating higher quality (ie, greater internal validity). All extracted data, as well as quality scores, were agreed to by 2 reviewers before the data could be entered.

Analyses

The end points for clinical efficacy and effectiveness were those considered to have most clinical relevance: the number of patients receiving red blood cell (RBC) transfusions from study entry to end of treatment, and QoL changes based on the Functional Assessment of Cancer Therapy–Fatigue (FACT-F) subscale[10] or any linear analog self-assessment (LASA) scale measuring overall fatigue and reporting pre- and posttreatment scores (or change in scores). The range of possible FACT-F scores is 0 to 52, and the range of possible LASA scale scores is 0 to 100, with higher scores reflecting improvement. For the purposes of these analyses, efficacy was defined as a reduction in RBC transfusions (compared with standard care or placebo comparators in clinical-trial settings), improvement in QoL (as measured using FACT-F, LASA, or comparable linear analog scales, such as visual analog scales [VAS] or the Cancer Linear Analogue Scale [CLAS]), or both. Effectiveness was defined using the same outcomes, but in real-world settings (ie, prospective community-based uncontrolled studies of ≥300 patients).

The safety outcomes were on-study deaths (all-cause and treatment-associated deaths) and the number of

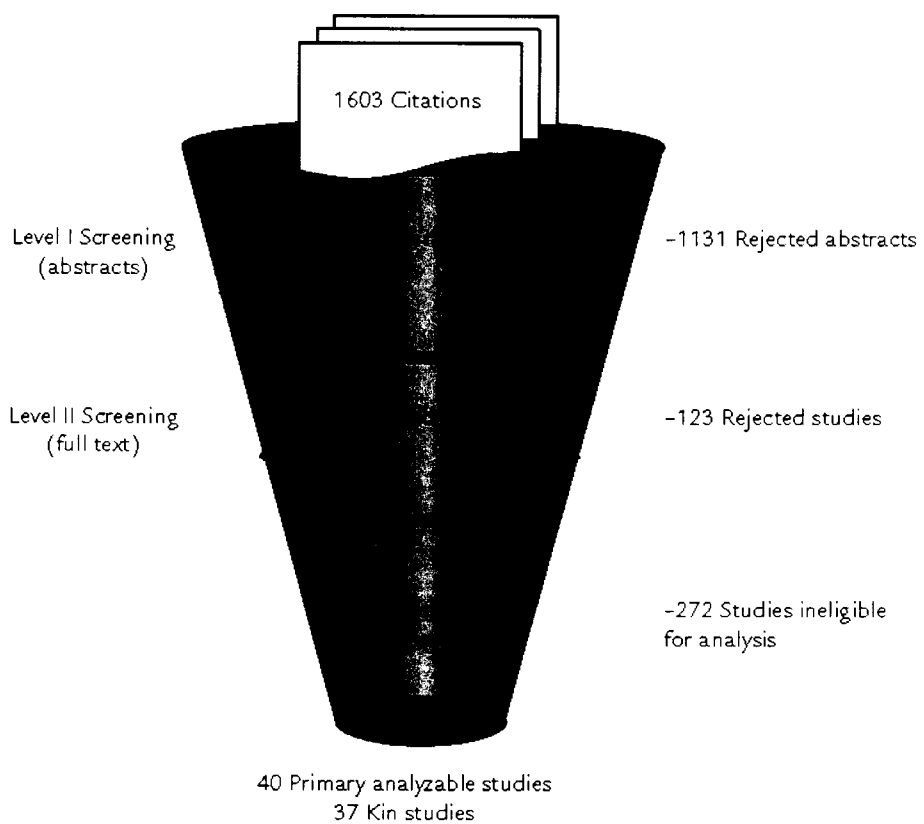


Figure 1. Study attrition in selection for meta-analysis of studies of epoetin and darbepoetin in patients with chemotherapy-induced anemia. Kin studies were additional publications describing the same patients, or a subset or superset of the main study population, appearing in other publications.

patients with VTE, which was defined differently across studies. VTE definitions included deep vein thrombosis, pulmonary embolism, or any other thromboembolic events occurring as a treatment-emergent event during study, regardless of type of event monitoring (ie, active or passive) or confirmation methods used (ie, clinical, radiographic, or pathologic).

Studies of primary interest were those using the following labeled dose regimens[11,12]: epoetin-alfa or epoetin-β (the latter of which is not approved in the United States), with doses that were fixed or ranging from 150 to 300 U/kg TIW or 40,000 to 60,000 U QW; and darbepoetin-alfa, with doses that were fixed or ranging from 2.25 to 4.50 μg/kg QW. To the extent that the data allowed, we examined the impact of recent (year-2004) product-label changes that recommended ceasing ESP treatment when Hb levels reached ≥13 g/dL.[6]

Study, patient, and treatment-level data were summarized using basic descriptive statistics (ie, simple counts and means). The number of patients randomized or enrolled was used as the denominator in the calculation of study and patient demographics. Two main analytic approaches were utilized to quantify the benefit and risk outcomes of interest. In the first approach, weighted means of frequencies of transfusions, VTE, and deaths, and absolute differences in pre- and posttreatment QoL scores (eg, FACT-F, LASA) were calculated. In the second approach, meta-analyses of within-study differences (eg, ESP vs control, epoetin vs darbepoetin-alfa) were conducted for frequencies of transfusions, VTE, and deaths, and for changes in QoL scores (ie, FACT-F and general [LASA/VAS/CLAS] scales standardized to a 0–100 common scale). Both fixed-effects models (FEM)[13,14] and random-effects models (REM)[15] were performed for each estimate. REM provides the more conservative methodology for combining results across studies, taking into consideration within- and between-study variation, and is therefore used preferentially in this report. Both REM and FEM are shown in Figures 2 through 7.

For studies in which categorical outcomes were meta-analyzed, results were expressed as an odds ratio (OR) with 95% CI in active-versus-control treatments. In such cases, OR <1 indicated a lower risk for active treatment than for control, and OR >1 indicated a greater risk for the active treatment than for the control. For studies in which continuous outcomes were meta-analyzed, results were expressed as a standardized mean difference with 95% CI. These mean differences within each study were standardized by dividing the difference between studies by the pooled SD of the difference between studies before the meta-analysis.

The extent of statistical heterogeneity was quantified using the Cochran Q test[16] and explored using sensitivity analyses, including jackknife analyses, meta-regression analyses,[17] and subgroup analyses, as appropriate. In particular, meta-regressions were run to test the impact of several study, patient, and treatment-level covariates on the percentage of patients transfused. There were insufficient data to perform similar regression analyses for QoL outcomes. Controlling for type of comparison (active vs control), the covariates used were geographic location, industry sponsorship, level of evidence, year of study, size of study, population in study (adult or pediatric), sex, age, baseline Hb, and type of tumor (solid or hematologic). These covariates were chosen based on clinical expertise, published literature, and availability of reporting across studies.

In the extraction of safety data, 0 was extracted only when reported. In the absence of data, 0 was not assumed. To include 0 event studies in the meta-analyses, 0.25 was used in the analyses wherever a 0 was extracted.

All calculations were performed using SAS software, version 8.1 (SAS Institute Inc., Cary, North Carolina), SPSS software, version 13.0 (SPSS Inc., Chicago, Illinois), and Comprehensive Meta-Analysis, version 2.0 (Biostat, Inc., Englewood, New Jersey).

RESULTS

Studies

A total of 40 studies including 21,378 patients met all eligibility criteria for these analyses. Study attrition from the literature search and screening process is summarized in Figure 1. As summarized in Table I and listed in Table II, there were 28 controlled trials (n = 8323) of epoetin, of which 10 (n = 5514) were direct comparisons with darbepoetin and 18 (n = 2809) were comparisons with standard care or placebo. In these 18 epoetin-versus-control studies, the study drug was epoetin-alfa in 10 and epoetin-β in 3, and was not specified in 5. There were also 6 uncontrolled studies of epoetin-alfa, epoetin-β, or unspecified epoetin product, with a total of 9771 patients. There were 4 controlled trials (n = 984) of darbepoetin-alfa (not including the epoetin comparison studies already

Table I. Characteristics of studies of epoetin (EPO) and darbepoetin (DARB) in chemotherapy-induced anemia in cancer patients.

				Controlled Studies											
	All Studies			EPO vs Control*			DARB vs Control*			DARB vs EPO			Uncontrolled Studies		
Variable	k	t	N	k	t	n	k	t	n	k	t	n	k	t	n
Total	40	89	21,378	18	43	2809	4	10	984	10	28	5514	8	8	12,071
Publication year															
1990–1999	12	29	5795	10	27	1083	0	0	0	0	0	0	2	2	4712
2000–2005	28	60	15,583	8	16	1726	4	10	984	10	28	5514	6	6	7359
Publication type															
Manuscript	32	75	14,654	17	41	2586	4	10	984	5	18	708	6	6	10,376
Abstract	8	14	6724	1	2	223	0	0	0	5	10	4806	2	2	1695
Study design															
RCT	30	77	6149	17	41	2789	4	10	984	9	26	2376	0	0	0
nRCT	2	4	3158	1	2	20	0	0	0	1	2	3138	0	0	0
UCS	8	8	12,071	0	0	0	0	0	0	0	0	0	8	8	12,071
Industry sponsored															
Yes	29	68	18,327	11	29	1954	4	10	984	7	22	3886	7	7	11,503
No	11	21	3051	7	14	855	0	0	0	3	6	1628	1	1	568
Quality score†															
1–3	15	45	2588	10	27	1880	0	0	0	5	18	708	0	0	0
4–5	10	22	1670	6	12	686	4	10	984	0	0	0	0	0	0
EPO type															
α	16	26	11,350	10	20	1579	0	0	0	0	0	0	6	6	9771
β	3	9	635	3	9	635	0	0	0	0	0	0	0	0	0
ESP mixed/unspecified	15	42	6109	5	14	595	0	0	0	10	28	5514	0	0	0
DARB	6	12	3284	0	0	0	4	10	984	0	0	0	2	2	2300

k = number of studies; t = number of treatment groups; n = number of patients; RCT = randomized controlled trial; nRCT = nonrandomized controlled trial; UCS = uncontrolled study; ESP = erythropoiesis-stimulating protein.

*Placebo or standard care (usually transfusions).

†Jadad score,[9] whereby points are assigned for description of randomization and blinding procedures, and for accounting for all withdrawals (higher numbers indicate higher quality and greater internal validity). Only RCTs in manuscript format were given a quality score.

Table II. Characteristics of epoetin (EPO) and darbepoetin (DARB) in chemotherapy-induced anemia studies that were included in the meta-analyses.

Study	Regimen	No. of Patients	Mean Age, Years	Tumor Type: Hematologic, No. of Patients	Tumor Type: Solid, No. of Patients	Chemotherapy	Mean Baseline Hb, g/dL	Duration, Weeks
EPO vs control*								
Abels[18]	EPO 100 U/kg TIW	63	NR	NR	NR	NR	9.8	NR
	Placebo TIW	55	NR	NR	NR	NR	9.2	NR
	EPO 150 U/kg TIW	79	NR	NR	NR	Nonplatinum regimens	9.5	NR
	Placebo TIW	74	NR	NR	NR	Nonplatinum regimens	9.8	NR
	EPO 150 U/kg TIW	64	NR	14	44	Platinum regimens	9.8	NR
	Placebo TIW	61	NR	9	51	Platinum regimens	9.5	NR
Aravantinos et al[19]	EPO 150 U/kg TIW	24	59	0	24	Platinum regimens	9.8	NR
	Standard care	23	64	0	23	Platinum regimens	9.3	NR
Boogaerts et al[20]	EPO 150–300 U/kg TIW	133	62	74	59	Various	9.0	NR
	Standard care	129	62	71	58	Various	9.2	NR
Cascinu et al[21]	EPO 100 U/kg TIW	50	58	0	50	Platinum regimens	8.6	9
	Placebo TIW	50	57	0	50	Platinum regimens	8.7	9
Cazzola et al[22]	Standard care	29	68	29	0	Nonplatinum regimens	9.5	NR
	EPO 1000 U QD	31	67	31	0	Nonplatinum regimens	9.3	NR
	EPO 2000 U QD	29	65	29	0	Nonplatinum regimens	9.4	NR
	EPO 5000 U QD	31	68	31	0	Nonplatinum regimens	9.4	NR
	EPO 10,000 U QD	26	63	26	0	Nonplatinum regimens	9.4	NR
Dammacco et al[23]	EPO 150–300 U/kg TIW	40	60.6	40	0	Nonplatinum regimens	8.7	NR
	No treatment	31	65	31	0	Nonplatinum regimens	8.3	NR
Dusenbery et al[24]	EPO 100–200 U/kg TIW to 5 times weekly	15	43	0	15	Platinum regimens	10.3	6
	No EPO treatment	5	53	0	5	Platinum regimens	10.7	6
Iconomou et al[25]	EPO 10,000–20,000 U TIW	61	60.6	0	61	Various	10.1	NR
	Standard care	61	62.6	0	61	Various	10.1	NR
Kurz et al[26]	EPO 150–300 U/kg TIW	23	54.4	0	23	Platinum	9.9	NR
	Placebo TIW	12	52.7	0	12	Platinum	9.9	NR
Littlewood et al[27]	EPO 150–300 U/kg TIW	251	58.3	115	136	Nonplatinum regimens	9.9	28
	Placebo TIW	124	59.5	58	66	Nonplatinum regimens	9.7	28

(continued)

Table II. (Continued)

Study	Regimen	No. of Patients	Mean Age, Years	Tumor Type: Hematologic, No. of Patients	Tumor Type: Solid, No. of Patients	Chemotherapy	Mean Baseline Hb, g/dL	Duration, Weeks
Oberhoff et al[28]	EPO 5000 U QD	117	53	0	117	Various	9.6	NR
	No EPO treatment	110	56	0	110	Various	10.3	NR
Porter et al[29]	EPO 150–300 U/kg TIW	12	14	0	12	Nonplatinum regimens	9.7	NR
	Placebo	12	13	0	12	Nonplatinum regimens	9.4	NR
Pronzato et al[30]	EPO 10,000–20,000 U TIW	111	53.2	0	89	Various	10.7	NR
	Standard care	112	54.5	0	89	Various	10.8	NR
Savonije et al[31]	EPO 10,000–20,000 U TIW	211	NR	0	211	Platinum regimens	10.7	NR
	Standard care	104	NR	0	104	Platinum regimens	10.8	NR
Varan et al[32]	EPO 150 U/kg TIW	17	NR	NR	NR	Various	8.5	NR
	No EPO treatment	17	NR	NR	NR	Various	8.5	NR
Wagner et al[33]	EPO 200 U/kg QD	18	3.2	0	18	Anthracycline-based regimens	8.9	NR
	G-CSF	20	3.2	0	20	Anthracycline-based regimens	9.4	NR
Witzig et al[34]	EPO 40,000–60,000 U QW	174	63.6	NR	NR	Various	9.5	NR
	Placebo	170	63.7	NR	NR	Various	9.4	NR
Wurnig et al[35]	EPO 600 U/kg BIW	15	NR	0	15	Nonplatinum regimens	10.9	NR
	Placebo BIW	15	NR	0	15	Nonplatinum regimens	10.9	NR
DARB vs control*								
Hedenus et al[36]	DARB 1 μg/kg QW	11	64	11	0	Various	9.7	16
	DARB 2.25 μg/kg QW	22	69	22	0	Various	9.4	16
	DARB 4.5 μg/kg QW	22	70	22	0	Various	9.7	16
	Placebo	11	63	11	0	Various	9.5	16
Hedenus et al[37]	DARB 2.25 μg/kg QW	176	64.8	176	0	Various	9.6	NR
	Placebo QW	173	64.6	123	0	Various	9.5	NR
Kotasek et al[38]	DARB 4.5–15 μg q3w	198	88.3	0	198	Various	9.9	NR
	Placebo q3w	51	56.2	0	51	Various	9.4	NR
Vansteenkiste et al[39]	DARB 2.25–4.5 μg/kg QW	159	61.6	0	156	Platinum regimens	10.3	16
	Placebo QW	161	61.3	0	158	Platinum regimens	9.9	16
EPO vs DARB								
Alexopoulos and Kotsori[40]	EPO 10,000–20,000 U TIW	25	NR	0	25	NR	9.8	NR
	DARB 150–300 μg QW	25	NR	0	25	NR	10.2	NR

(continued)

Table II. (Continued)

Study	Regimen	No. of Patients	Mean Age, Years	Tumor Type: Hematologic, No. of Patients	Tumor Type: Solid, No. of Patients	Chemotherapy	Mean Baseline Hb, g/dL	Duration, Weeks
Fahrbach et al[41]	EPO, dosage NR	2954	NR	NR	NR	Various	11.0	NR
	DARB, dosage NR	184	NR	NR	NR	Various	11.0	NR
Glaspy et al[42]	EPO 40,000 U QW	607	63.7	0	603	Platinum regimens	10.2	NR
	DARB 200 μg q2w	613	63.2	0	606	Platinum regimens	10.2	NR
Glaspy et al[43]	DARB 0.5 μg/kg QW	13	NR	0	13	Various	11.0	NR
	DARB 1 μg/kg QW	36	NR	0	36	Various	11.0	NR
	DARB 1.5 μg/kg QW	35	NR	0	35	Various	11.0	NR
	DARB 2.25 μg/kg QW	59	NR	0	59	Various	11.0	NR
	DARB 4.5 μg/kg QW	29	NR	0	29	Various	11.0	NR
	DARB 6 μg/kg QW	30	NR	0	30	Various	11.0	NR
	DARB 8 μg/kg QW	14	NR	0	14	Various	11.0	NR
	EPO 150–300 U/kg QW	53	57.8	0	53	Various	10.0	NR
Glaspy et al[44]	DARB 1.5–4.5 μg/kg QW	32	60.5	0	32	Various	9.5	NR
	DARB 2.25–4.5 μg/kg QW	32	66.4	0	32	Various	9.9	NR
	DARB 3–4.5 μg/kg QW	32	62.7	0	30	Various	9.9	NR
	EPO 40,000 U TIW	31	63.5	0	31	Various	9.8	NR
Jakubowski et al[45]	EPO 40,000–60,000 U QW	24	NR	0	24	NR	10.2	NR
	DARB 200–300 μg q2w	16	NR	0	16	NR	10.0	NR
Schwartzberg et al[46]								
Study 1	DARB 200–300 μg q2w	72	NR	0	72	Various	10.5	NR
	EPO 40,000–60,000 U QW	69	NR	0	69	Various	10.6	NR
Study 2	DARB 200–300 μg q2w	51	NR	0	51	Various	10.4	NR
	EPO 40,000–60,000 U QW	51	NR	0	51	Various	10.4	NR
Study 3	DARB 200–300 μg q2w	34	NR	0	34	Various	10.1	NR
	EPO 40,000–60,000 U QW	35	NR	0	35	Various	10.3	NR
Waltzman et al[47]	EPO 40,000 U QW	178	NR	0	178	Platinum regimens	10.2	16
	DARB 200 μg q2w	180	NR	0	180	Platinum regimens	10.1	16
EPO alone								
Demetri et al[48]	EPO 10,000–20,000 U TIW	2370	63	515	1797	Various	9.3	NR
Gabrilove et al[49]	EPO 40,000–60,000 U QW	3012	63.1	497	2428	Various	9.5	16

(continued)

Table II. (Continued)

Study	Regimen	No. of Patients	Mean Age, Years	Tumor Type: Hematologic, No. of Patients	Tumor Type: Solid, No. of Patients	Chemotherapy	Mean Baseline Hb, g/dL	Duration, Weeks
Gisselbrecht et al[50]	EPO 40,000 U QW	568	NR	568	0	NR	10.5	NR
Glaspy et al[51]	EPO 150–300 U/kg TIW	2342	62.2	467	1563	Various	9.2	NR
Reinhardt et al[52]	EPO 10,000 U TIW	702	58.5	49	596	Nonplatinum regimens	10.1	NR
Shasha et al[53]	EPO 40,000–60,000 U QW	777	61.7	8	434	Platinum regimens	9.9	NR
DARB alone								
Gabrilove et al[54]	DARB 200–300 μg q2w	1127	NR	NR	NR	Various	10.1	NR
Vadhan-Raj et al[55]	Darbepoetin 3–5 μg/kg q2w	1173	59	148	1025	Platinum regimens	10.4	NR

Hb = hemoglobin; NR = not reported; G-CSF = granulocyte colony–stimulating factor; q3w = every 3 weeks; q2w = every 2 weeks.
*Placebo or standard care (usually transfusions).

noted), and 2 uncontrolled studies (n = 2300) of darbepoetin-alfa. Quality scores[9] were assigned to 25 RCTs that were published as full papers; of these, fewer than half (6 epoetin and 4 darbepoetin) scored 4 or 5 points. All but one[25] (which compared epoetin with standard of care) of these 10 studies utilized placebo comparators. Industry sponsorship was identifiable in 29 of the 40 studies. Studies excluded from this meta-analysis are noted in Appendix I.

Epoetin schedules ranged widely from daily to once-weekly administration, with weight-based unit doses ranging from 100 to 600 U/kg, and fixed doses ranging from 1000 to 60,000 U. Darbepoetin-alfa schedules also ranged widely from weekly to once-per-3-weeks administration, and weight-based doses ranged from 1 to 15 μg/kg. Epoetin was administered at dosages of 150 to 300 U/kg SC TIW in 11 epoetin groups in controlled trials, and in only 1 group in the uncontrolled trials. Once-weekly dose frequency (at 40,000–60,000 U per dose) for epoetin was reported in another 10 groups in controlled trials, and 3 groups in uncontrolled trials. Other doses and other frequencies were noted in the remainder of the epoetin studies. As for darbepoetin-alfa, dose schedules per the US product label (2.25–4.5 μg/kg QW) were reported in 7 groups in the controlled trials and none of the uncontrolled trials.

As noted previously, the baseline Hb requirement for patients in CIA studies was <11 g/dL. Mean baseline Hb was comparable across studies, with means ranging from 9.6 g/dL in the epoetin-versus-control studies to 10.4 g/dL in the epoetin–versus–darbepoetin-alfa studies. In the darbepoetin-alfa–versus–control studies, mean baseline Hb was 9.7 g/dL. In the uncontrolled studies of epoetin, mean baseline Hb was 9.8 g/dL; in the darbepoetin-alfa uncontrolled studies, it was 10.2 g/dL.

The Hb at which ESP was to be discontinued was often not reported, but when discernible, it ranged from 12 to 15 g/dL in the studies that reported this information. In accordance with current safety instructions in the product labels of both epoetin and darbepoetin-alfa, it is important to note that only 10 of the 40 total studies reported requiring the discontinuation of ESP if Hb exceeded 13 g/dL. Finally, the use of iron therapy was only occasionally mentioned as an option to be added to treatment regimens if serum ferritin was low, but serum ferritin or other measures of iron stores were rarely reported. Similarly, serum erythropoietin levels were rarely reported.

Clinical Efficacy and Effectiveness

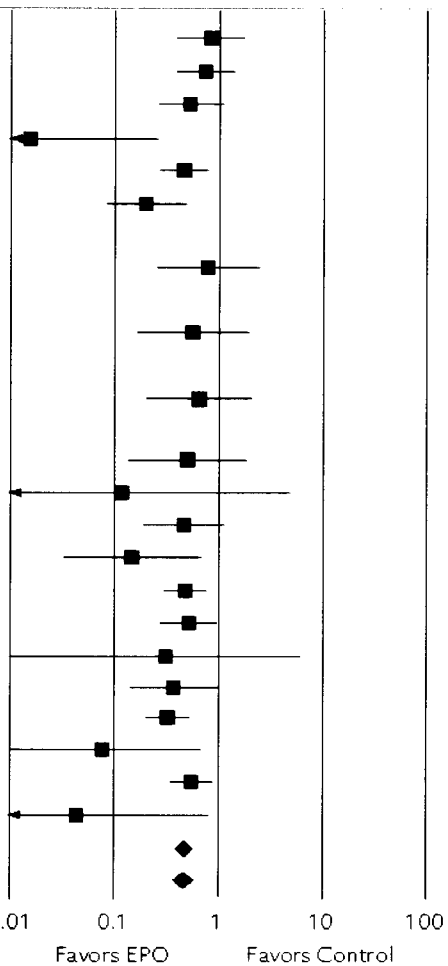
The proportion of epoetin patients receiving RBC transfusions (from study start to study end) was significantly reduced compared with same-study control patients (26.6% vs 48.8%; OR, 0.44 [95% CI, 0.35–0.55]; Figure 2; Table III). In darbepoetin-alfa–versus–control studies, transfusion frequencies from start to end of the study could not be obtained because transfusions were reported only for week 5 to study end. However, for the 3 studies with transfusion results for this interval,[37–39] a significant advantage for darbepoetin-alfa relative to controls was demonstrated; the OR for transfusion in darbepoetin-alfa patients compared with controls was 0.41 (95% CI, 0.31–0.55). Finally, in the 5 studies comparing epoetin with darbepoetin-alfa that reported transfusion outcomes (study start to study end), the transfusion frequencies were not significantly different: 18.6% among epoetin patients and 22.8% among darbepoetin-alfa patients, for an OR of 0.77 (95% CI, 0.58–1.02). Study duration was not always reported, but when it could be determined, the mean duration was 6 to 28 weeks for studies comparing epoetin with control, 16 weeks for studies comparing darbepoetin-alfa with control, 16 weeks for studies comparing epoetin with darbepoetin-alfa, and 13 to 16 weeks for uncontrolled studies. Given the general comparability of these durations, plus the fact that within-study measures of relative treatment differences were used (ie, OR), study duration was not expected to be an important confounder in these analyses.

When only labeled (or commonly used) doses were examined, the mean transfusion frequencies in epoetin groups between study start to study end were 39% for doses of 150 to 300 U/kg TIW and 16% to 26% for doses of 40,000 to 60,000 U QW. The comparable transfusion rate in darbepoetin-alfa studies using 200 μg once every 2 weeks was 20%, and there were no comparable transfusion data available for studies using regimens of 2.25 to 4.5 μg per week.

Meta-regressions using the log OR for the percentage of patients transfused and controlling for type of comparison (active vs control) examined the effect of geographic location, industry sponsorship, level of evidence, year of study, size of study, population in study (adult or pediatrics), sex, age, baseline Hb, and type of tumor (solid or hematologic). None was significant. It should be noted that although this was a relatively small group of studies, even when these covariates

Figure 2. Meta-analysis of transfusion incidence in studies comparing epoetin (EPO) with control (placebo or standard care [usually transfusions]) in patients with chemotherapy-induced anemia. Transfusion rate shown as number of patients in group who were transfused divided by all patients in group.

Source	Transfusion Rate EPO	Control	OR (95% CI)	P
Abels,[18] comparison 1	21/63	21/55	0.81 (0.38–1.72)	0.583
Abels,[18] comparison 2	32/79	36/74	0.72 (0.38–1.36)	0.312
Abels,[18] comparison 3	34/64	42/61	0.51 (0.25–1.07)	0.073
Aravantinos et al[19]	9/24	23/23	0.01 (0.00–0.24)	0.004
Boogaerts et al[20]	43/104	67 /109	0.44 (0.26–0.77)	0.004
Cascinu et al[21]	10/50	28/49	0.19 (0.08–0.46)	0.000
Cazzola et al,[22] comparison 1	7/31	8/29	0.77 (0.24–2.47)	0.655
Cazzola et al,[22] comparison 2	5/29	8/29	0.55 (0.16–1.93)	0.348
Cazzola et al,[22] comparison 3	6/31	8/29	0.63 (0.19–2.11)	0.453
Cazzola et al,[22] comparison 4	4/26	8/29	0.48 (0.13–1.82)	0.280
Dusenbery et al[24]	0/15	1/5	0.11 (0.00–5.05)	0.258
Iconomou et al[25]	9/57	16/55	0.46 (0.18–1.15)	0.095
Kurz et al[26]	5/23	8/12	0.14 (0.03–0.66)	0.013
Littlewood et al[27]	62/244	49/115	0.46 (0.29–0.73)	0.001
Oberhoff et al[28]	26/101	36/88	0.50 (0.27–0.93)	0.028
Porter et al[29]	9/10	10/10	0.30 (0.01–8.33)	0.479
Pronzato et al[30]	6/89	15/89	0.36 (0.13–0.97)	0.043
Savonije et al[31]	77/211	66/102	0.31 (0.19–0.51)	0.000
Varan et al[32]	1/17	8/17	0.07 (0.01–0.66)	0.020
Witzig et al[34]	42/164	65/166	0.54 (0.34–0.86)	0.009
Wurnig et al[35]	8/15	14/14	0.04 (0.00–0.78)	0.033
Fixed-effects model			0.45 (0.38–0.53)	0.000
Random-effects model			0.44 (0.35–0.55)	0.000



OR = odds ratio.

were examined as individual covariates, they had no effect on the OR for RBC transfusions.

Epoetin patients in controlled trials had a statistically significant advantage in changes in FACT-F scores compared with control patients. The standardized mean difference between epoetin and control groups was 0.23 (95% CI, 0.10–0.36; $P < 0.001$) (Figure 3). Although there were no available trials comparing darbepoetin and control that had extractable FACT-F results, there were 2 such studies comparing epoetin and darbepoetin. There was no significant difference between epoetin and darbepoetin-alfa in FACT-F change scores in these studies (Table IV).

Table IV also shows meta-analytic results of QoL assessments using LASA scales (general LASA, VAS, and CLAS combined and standardized to a 0–100 scale). There was a significant advantage in QoL for epoetin patients compared with controls, as measured by LASA scores ($P < 0.001$).

In large, uncontrolled, community-based studies, the proportion of epoetin patients receiving RBC transfusions (8.6%) was smaller than the proportion noted in

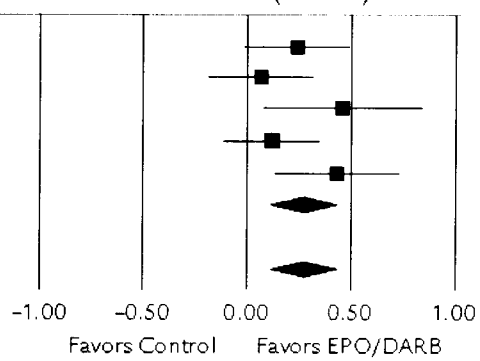
Table III. Transfusion outcomes in studies of epoetin (EPO) and darbepoetin (DARB) in chemotherapy-induced anemia in cancer patients.

Study Type	No. of Studies	Transfusion Rate, % (SEM)*	OR (95% CI)†
EPO vs control	16[18-22,24-32,34,35]		0.44 (0.35–0.55)
EPO		26.6 (5.30)	
Control‡		48.8 (6.71)	
DARB vs EPO	5[40,42,45-47]		0.77 (0.58–1.02)
DARB		22.8 (7.80)	
EPO		18.6 (3.90)	
EPO alone	3[48,51,52]	8.6 (11.70)	–
DARB alone	1[55]	26.0	–

OR = odds ratio.
*Calculated as number of patients in group who were transfused, divided by all patients in group.
†Calculated using a random-effects model.
‡Placebo or standard care (usually transfusions).

Figure 3. Functional Assessment of Cancer Therapy–Fatigue subscale[10] changes in studies comparing epoetin (EPO) or darbepoetin (DARB) with control (placebo or standard care [usually transfusions]) in patients with chemotherapy-induced anemia.*

Source	Comparison	Difference in Mean Values (95% CI)	P
Littlewood et al[27]	EPO vs control	0.23 (–0.02 to 0.48)	0.076
Boogaerts et al[20]	EPO vs control	0.11 (–0.16 to 0.38)	0.428
Iconomou et al[25]	EPO vs control	0.44 (0.07–0.82)	0.021
Witzig et al[34]	EPO vs control	0.11 (–0.12 to 0.33)	0.360
Savonije et al[31]	DARB vs control	0.42 (0.12–0.71)	0.005
Fixed-effects model	EPO & DARB vs control	0.22 (0.10–0.34)	0.000
Random-effects model	EPO & DARB vs control	0.23 (0.10–0.36)	0.001



*Range of possible scores, 0–52.

controlled trials of epoetin (26.6%). In the single uncontrolled trial of darbepoetin-alfa in which patients' transfusion results were reported, the rate was 26.0%, compared with the rate of 22.8% noted among patients who received darbepoetin-alfa in studies comparing that agent with epoetin (Table III).

QoL improvements (as reflected in FACT-F scores) were not available in epoetin patients in uncontrolled community studies. LASA results were, however, available, and the magnitude of improvement was larger in community studies than in controlled trials of epoetin (increases of 11.3 and 4.6, respectively). For darbepoetin-alfa, no LASA results were available in uncontrolled studies, but in a single uncontrolled study with FACT-F, the magnitude of improvement was similar to that seen in controlled trials of darbepoetin-alfa (increases of 4.9 and 4.5, respectively; Table IV).

Table IV. Quality-of-life outcomes in studies of epoetin (EPO) and darbepoetin (DARB) in chemotherapy-induced anemia in cancer patients.

	FACT-F				LASA			
Study Type	No. of Studies	Mean Change	Mean Difference (95% CI)	*P*	No. of Studies	Mean Change	Mean Difference (95% CI)	*P*
EPO *vs* control	4[20,25,27,31,34]		0.23 (0.10–0.36)	<0.001	4[20,25,27,31]		0.36 (0.14–0.57)	<0.001
EPO		3.4				4.8		
Control*		-0.8				-3.6		
DARB *vs* control	0		–		0		–	–
DARB		–				–		
Control*		–				–		
DARB *vs* EPO	2[42,44]		-0.06 (-0.17 to 0.04)	NS	0		–	–
DARB		5.6				–		
EPO		2.0				–		
EPO alone	0	–	–	–	5[48,51-54]	11.3	–	–
DARB alone	1[55]	4.9	–	–	0	–	–	–

FACT-F = Functional Assessment of Cancer Therapy–Fatigue subscale[10] (range of possible scores, 0–52); LASA = linear analog self-assessment scale (range of possible scores, 0–100).
*Placebo or standard care (usually transfusions).

Risk of VTE and Death

The frequency of VTE in studies comparing epoetin with placebo or standard care was 5.2% among epoetin patients and 3.1% among control patients, for an OR of 1.41 (95% CI, 0.81–2.47). In the sole similarly controlled trial of darbepoetin-alfa that reported VTE, the frequency was 4.4% among darbepoetin-alfa patients and 3.1% among control patients, for an OR of 1.44 (95% CI, 0.45–4.63; Table V; Figure 4). When all trials comparing ESP agents with controls were meta-analyzed, the change in risk was not statistically significant (OR, 1.41 [95% CI, 0.81–2.47]; Figure 4).

In the single direct-comparison trial of epoetin and darbepoetin-alfa that reported VTE events, 7.0% of epoetin patients and 5.9% of darbepoetin-alfa patients experienced VTE, for a nonsignificant OR of 1.19 (95% CI, 0.72–1.65). In uncontrolled trials of epoetin, the mean VTE rate for epoetin was 3.3%, which appeared to be slightly lower than the mean VTE rate in the controlled trials of epoetin. The VTE frequency in darbepoetin-alfa patients in the single uncontrolled trial with this information (0.9%) was also lower than that observed in controlled trials.

It should be noted that VTE, when reported, had a narrow range of frequencies (0%–7%), except for Dusenbery et al[24]—in that study, the VTE rate in epoetin patients was 26.7%. In this study, however, epoetin was administered 5 times weekly (ie, not per product labeling instructions). When only labeled dose schedules were examined, there were no reports of VTE in epoetin groups receiving 150 to 300 U TIW, and there was only 1 controlled study of ESP that reported VTE in epoetin groups receiving 40,000 U QW.[34] In that study, the frequency of VTE was 4.8%. In a further study of epoetin versus darbepoetin-alfa,[42] the frequency of VTE among those receiving epoetin 40,000 U QW was 7.0%. Only 1 darbepoetin-alfa group receiving the labeled dose reported VTE,[39] with a VTE frequency of 4.4% in darbepoetin-alfa patients receiving 2.25 to 4.5 μg/kg QW. There was only 1 other study[42] that reported VTE in darbepoetin-alfa patients. In this study, the VTE frequency was 5.9% in patients receiving darbepoetin 200 μg Q2W.

The impact on VTE risk of recent label changes recommending stopping ESP at Hb of 13 or higher could not be readily assessed, due to the fact that only 10 of 40 studies in this review reported using this rule, and

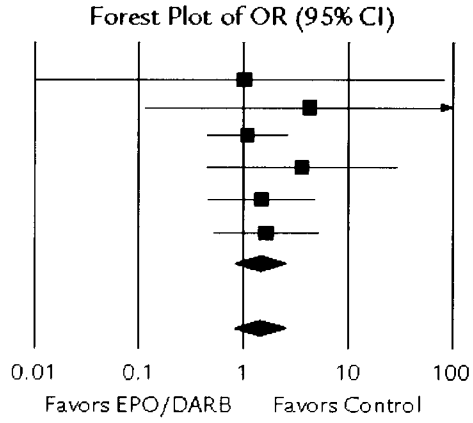
Table V. Selected adverse events in studies of epoetin (EPO) and darbepoetin (DARB) in chemotherapy-induced anemia in cancer patients.

	VTEs			All-Cause Mortality		
Study Type	No. of Studies	Rate, % (SEM)*	OR (95% CI)†	No. of Studies	Rate, % (SEM)*	OR (95% CI)†
EPO vs control	5[21,24,27,31,34]		1.41 (0.81–2.47)	8[23,24,27-29,32,34,35]		0.86 (0.58–1.28)
EPO		5.2 (0.99)			10.3 (4.21)	
Control‡		3.1 (0.68)			10.6 (5.13)	
DARB vs control	1[39]		1.44 (0.45–4.63)	3[36,38,39]		1.26 (0.74–2.14)
DARB		4.4			7.3 (2.52)	
Control‡		3.1			6.8 (2.11)	
DARB vs EPO	1[42]		1.19 (0.72–1.65)	1[47]		0.81 (0.21–1.40)
DARB		5.9			15.6	
EPO		7.0			12.9	
EPO alone	2[49,52]	3.3 (1.14)	–	5[48,49,51-53]	9.9 (3.72)	–
DARB alone	1[55]	0.9	–	1[55]	5.0	–

VTEs = venous thromboembolic events; OR = odds ratio.
*Calculated as number of patients in group who experienced this event divided by all patients in group.
†Calculated using a random-effects model.
‡Placebo or standard care (usually transfusions).

Figure 4. Incidence of venous thromboembolism (VTE) in studies comparing epoetin (EPO) or darbepoetin (DARB) with control (placebo or standard care [usually transfusions]) in patients with chemotherapy-induced anemia.

		VTE Rate			
Source	Comparison	Study Drug	Control	OR (95% CI)	*P*
Cascinu et al[21]	EPO vs control	0/50	0/50	1.00 (0.01–81.47)	1.000
Dusenbery et al[24]	EPO vs control	4/15	0/5	4.18 (0.14–128.81)	0.413
Littlewood et al[27]	EPO vs control	17/251	8/124	1.05 (0.44–2.51)	0.907
Savonije et al[31]	EPO vs control	7/211	1/104	3.53 (0.43–29.11)	0.241
Vansteenkiste et al[39]	DARB vs control	7/159	5/161	1.44 (0.45–4.63)	0.543
Witzig et al[34]	EPO vs control	8/168	5/165	1.60 (0.51–5.00)	0.418
Fixed-effects model	EPO & DARB vs control			1.41 (0.81–2.47)	0.226
Random-effects model	EPO & DARB vs control			1.41 (0.81–2.47)	0.226



OR = odds ratio.

of these studies, none reported VTE. On the other hand, the impact of baseline Hb could be assessed. In post hoc analyses of VTE frequencies in studies with higher baseline Hb levels (>11 g/dL) (Figure 5; Appendix II), these non-CIA treatment (NCIAT) studies yielded a nonsignificant OR of 1.41 (95% CI, 0.72–2.78), for risk of VTE among those receiving ESP rather than control, which was similar to the OR of 1.41 (95% CI, 0.81–2.47) in CIA studies, suggesting VTE risk with ESPs may not have been affected by the initial Hb level.

Finally, all-cause mortality during the study period in controlled CIA trials comparing epoetin with placebo or standard care was 10.3% among epoetin patients and 10.6% among control patients, for an OR of 0.86 (95% CI, 0.58–1.28). In similarly controlled studies of darbepoetin-alfa, all-cause mortality during the study period was 7.3% among darbepoetin-alfa patients and 6.8% among control patients, for an OR of 1.26 (95% CI, 0.74–2.14). These results did not reach statistical significance in either case (Table V, Figure 6). In the single direct-comparison trial of epoetin versus darbepoetin-alfa, all-cause, on-study mortality was 12.9% in the epoetin group and 15.6% in the darbepoetin-alfa group, for an OR of 0.81 (95% CI, 0.21–1.40). In the uncontrolled community studies, all-cause mortality rates were slightly lower than in the controlled trial reports and lower in darbepoetin-alfa patients (5.0%) than in epoetin patients (9.9%).

The impact on mortality of recently added label recommendations to cease ESP at Hb ≥13 g/dL in patients with CIA could not be assessed due to insufficient reporting. However, post hoc analyses of the effect of baseline Hb on mortality rates were possible using NCIAT studies. Meta-analysis of these NCIAT studies revealed a nonsignificant OR of 1.39 (95% CI, 0.96–2.00) for ESP versus control on-study deaths; in CIA studies, the risk of on-study deaths for ESP groups versus control groups was also not significant, with an OR of 0.99 (95% CI, 0.72–1.36; Figure 7).

DISCUSSION

Each ESP in the studies included in this review showed efficacy, relative to standard care or placebo, in the treatment of CIA in cancer patients. Furthermore, 10 direct-comparison studies were also available in the literature (or in recent meeting abstracts), in which no clear superiority of one agent over another was established for the most clinically relevant outcomes (ie, transfusions and QoL).

It is important to note that the inclusion of community-based, uncontrolled studies of these agents supported the finding of ESP effectiveness in real-world treatment settings. Transfusion rates for epoetin in such studies appeared to be lower (8.6%) than in the controlled trials of epoetin (26.6%); we can only speculate that this observed difference may be related to different rules for transfusions at different study sites and in the different time intervals of these studies. The FACT-F results could not be compared across study design types because there were no community studies that measured FACT-E The LASA score improvement, however, was available in both controlled trials of epoetin (4.6) and community studies of epoetin (11.3). It is reassuring that transfusion frequencies and QoL measures were at least no worse in real-world settings than in controlled trial settings.

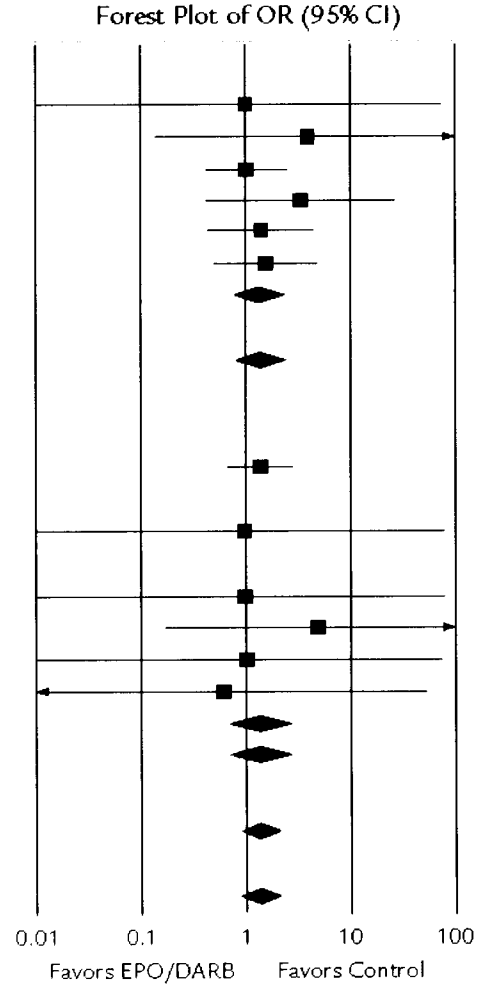
The evidence base is now stronger than in previous reviews with regard to demonstrating improvement in QoL in patients receiving these agents for CIA. The major previous reviews[67,68] did not provide quantitative estimates of QoL change. The magnitude of change before and after treatment with ESP met or exceeded the minimally clinically important difference for FACT-F of 3.0 points,[10,69] suggesting that treatment may have provided a real benefit to patients.

When considering the relative efficacy and safety of epoetin and darbepoetin-alfa, the wide range of dosage regimens used in these comparative studies should be considered. For instance, the Glaspy et al[43] study was a dose-finding study of 7 darbepoetin-alfa doses (0.5–8.0 μg/kg per week), ranging well below and well above the current label dose range, yet all compared with the label dose of epoetin (150 to 300 U/kg TIW). Furthermore, Hb criteria for cessation of ESP treatment were not reported sufficiently often or consistently enough to be amenable to analysis of their impact on treatment safety. Given this substantive between-study variability, the most reasonable comparisons of these products in the future would be limited to studies performed per current labeling or with commonly used doses and schedules.

This is particularly important given the fact that 2 studies[63,70] recently introduced serious concerns about the safety of ESP use in cancer patients. However, neither of these trials administered ESP in accordance with current product labels. Both used ESPs in cancer patients who were not anemic, and continued treatment until patients reached Hb thresh-

Figure 5. Incidence of venous thromboembolism (VTE) in studies comparing epoetin (EPO) or darbepoetin (DARB) with control (placebo or standard care [usually transfusions]) in patients with chemotherapy-induced anemia (CIA) or in patients without CIA (NCIA).

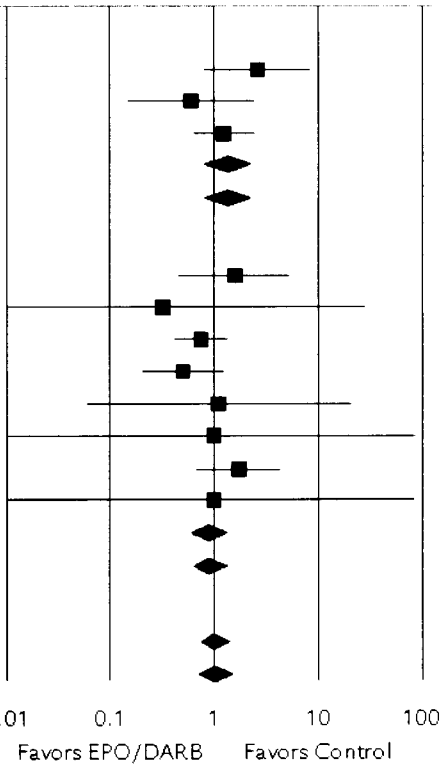
		VTE Rate			
Source	Comparison	Study Drug	Control	OR (95% CI)	*P*
CIA trials					
Cascinu et al[21]	EPO vs control	0/50	0/50	1.00 (0.01–81.47)	1.000
Dusenbery et al[24]	EPO vs control	4/15	0/5	4.18 (0.14–128.81)	0.413
Littlewood et al[27]	EPO vs control	17/251	8/124	1.05 (0.44–2.51)	0.907
Savonije et al[31]	EPO vs control	7/211	1/104	3.53 (0.43–29.11)	0.241
Vansteenkiste et al[39]	DARB vs control	7/159	5/161	1.44 (0.45–4.63)	0.543
Witzig et al[34]	EPO vs control	8/168	5/165	1.60 (0.51–5.0)	0.418
Fixed-effects model	EPO & DARB vs control			1.41 (0.81–2.47)	0.226
Random-effects model	EPO & DARB vs control			1.41 (0.81–2.47)	0.226
NCIA trials					
Chang et al[56]	EPO vs control	19/175	14/175	1.40 (0.68–2.89)	0.362
de Campos et al,[57] comparison 1	EPO vs control	0/12	0/12	1.00 (0.01–86.28)	1.000
de Campos et al,[57] comparison 2	EPO vs control	0/12	0/12	1.00 (0.01–86.28)	1.000
Kronberger et al[58]	EPO vs control	2/37	0/37	5.23 (0.17–160.83)	0.344
Rades et al[59]	EPO vs control	0/30	0/30	1.00 (0.01–82.45)	1.000
Wolchok et al[60]	EPO vs control	0/21	0/13	0.61 (0.01–51.77)	0.828
Fixed-effects model	EPO vs control			1.41 (0.72–2.78)	0.316
Random-effects model	EPO vs control			1.41 (0.72–2.78)	0.316
All trials					
Fixed-effects model	EPO & DARB vs control			1.41 (0.92–2.18)	0.116
Random-effects model	EPO & DARB vs control			1.41 (0.92–2.18)	0.116



OR = odds ratio.

Figure 6. Deaths during studies comparing epoetin (EPO) or darbepoetin (DARB) with control (placebo or standard care) in patients with chemotherapy-induced anemia.

Source	Death Rate: Study Drug	Death Rate: Control	OR (95% CI)	P
DARB vs control				
Hedenus et al[36]	10/174	4/170	2.53 (0.78–8.23)	0.123
Kotasek et al[38]	7/198	3/51	0.59 (0.15–2.35)	0.451
Vansteenkiste et al[39]	22/159	19/161	1.20 (0.62–2.32)	0.586
Fixed-effects model			1.26 (0.74–2.14)	0.398
Random-effects model			1.26 (0.74–2.14)	0.398
EPO vs control				
Dammacco et al[23]	9/40	5/31	1.51 (0.45–5.07)	0.505
Dusenbery et al[24]	0/15	0/5	0.32 (0.00–28.54)	0.615
Littlewood et al[27]	34/251	22/124	0.73 (0.40–1.31)	0.285
Oberhoff et al[28]	8/114	14/104	0.49 (0.20–1.21)	0.120
Porter et al[29]	1/10	1/11	1.11 (0.06–20.49)	0.944
Varan et al[32]	0/17	0/17	1.00 (0.01–84.36)	1.000
Witzig et al[34]	13/168	8/165	1.65 (0.66–4.08)	0.282
Wurnig et al[35]	0/15	0/14	0.93 (0.01–79.32)	0.975
Fixed-effects model			0.86 (0.58–1.28)	0.451
Random-effects model			0.86 (0.58–1.28)	0.451
Overall				
Fixed-effects model			0.99 (0.72–1.36)	0.925
Random-effects model			1.00 (0.69–1.44)	0.984



OR = odds ratio.

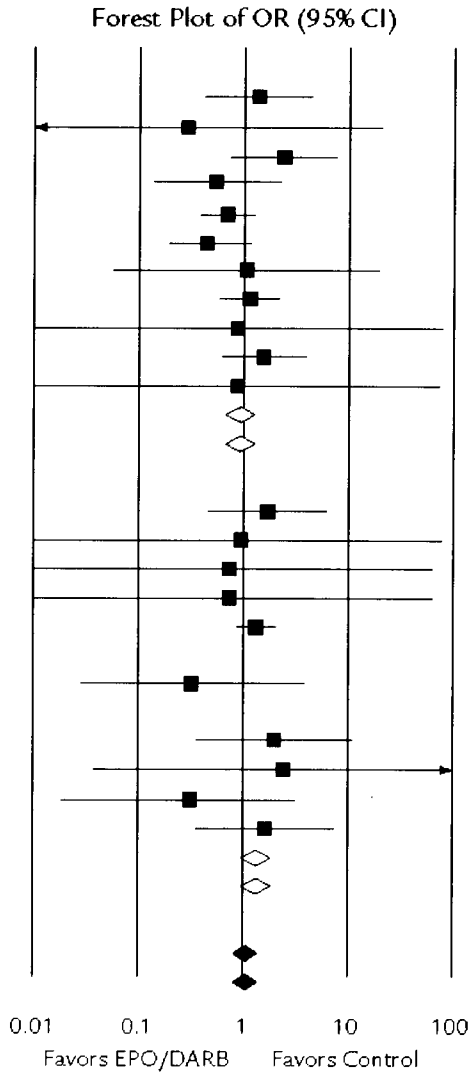
olds ~15 g/dL (ie, higher than those currently recommended). Although the results of these trials indicate the importance of remaining vigilant for unexpected adverse events in all patients, they do not necessarily provide hard evidence of risk with ESPs when they are used according to current product labels.[6]

For more than 10 years, investigators have tried to identify useful predictors of response to ESPs.[71] In an attempt to answer this question using data that are readily available and consistently reported in the studies included in this review, meta-regression analyses were run to assess the impact of numerous covariates on transfusion outcomes. None of the variables were significant predictors. Even the role of iron could not be assessed with these data, despite its potential utility, due to incomplete reporting. These models do not have great statistical power, however, because the missing data eliminated many studies. At this time, there remains no conclusive evidence to support the everyday use of any predictors of transfusion outcomes with either epoetin or darbepoetin-alfa.

Nevertheless, this review contributes several important findings to the body of evidence on ESP use in CIA patients. These include confirmation of the efficacy of darbepoetin-alfa, and that of all ESPs in patients with Hb <11 g/dL. These results were not included in an earlier Blue Cross/Blue Shield review by Seidenfeld et al,[67] which, in stratified analyses, found evidence for epoetin benefit only in patients with Hb <10 g/dL. Because that report also formed the basis of ASCO and ASH guidelines[1] on the use of ESPs in patients with cancer, recommendations for use in patients with Hb <11 g/dL

Figure 7. Deaths during studies comparing epoetin (EPO) or darbepoetin (DARB) with control (placebo or standard of care) in patients with chemotherapy-induced anemia (CIA) or in patients without CIA (NCIA).

Source	Comparison	Death Rate: Study Drug	Death Rate: Control	OR (95% CI)	P
CIA trials					
Dammacco et al[23]	EPO vs control	9/40	5/31	1.51 (0.45–5.07)	0.505
Dusenbery et al[24]	EPO vs control	0/15	0/5	0.32 (0.00–28.54)	0.615
Hedenus et al[36]	DARB vs control	10/174	4/170	2.53 (0.78–8.23)	0.123
Kotasek et al[38]	DARB vs control	7/198	3/51	0.59 (0.15–2.35)	0.451
Littlewood et al[27]	EPO vs control	34/251	22/124	0.73 (0.40–1.31)	0.285
Oberhoff et al[28]	EPO vs control	8/114	14/104	0.49 (0.20–1.21)	0.120
Porter et al[29]	EPO vs control	1/10	1/11	1.11 (0.06–20.49)	0.944
Vansteenkiste et al[39]	DARB vs control	22/159	19/161	1.20 (0.62–2.32)	0.586
Varan et al[32]	EPO vs control	0/17	0/17	1.00 (0.01–84.36)	1.000
Witzig et al[34]	EPO vs control	13/168	8/165	1.65 (0.66–4.08)	0.282
Wurnig et al[35]	EPO vs control	0/15	0/14	0.93 (0.01–79.32)	0.975
Fixed-effects model	EPO & DARB vs control			0.99 (0.72–1.36)	0.925
Random-effects model	EPO & DARB vs control			0.99 (0.72–1.36)	0.925
NCIA trials					
Bamias et al[61]	EPO vs control	7/72	4/72	1.83 (0.51–6.55)	0.352
Gamucci et al,[62] comparison 1	EPO vs control	0/21	0/21	1.00 (0.01–83.51)	1.000
Gamucci et al,[62] comparison 2	EPO vs control	0/21	0/17	0.81 (0.01–67.64)	0.924
Gamucci et al,[62] comparison 3	EPO vs control	0/21	0/17	0.81 (0.01–67.64)	0.924
Henke et al[63]	EPO vs control	109/180	89/171	1.41 (0.93–2.16)	0.109
ten Bokkel Huinink et al,[64] comparison 1	EPO vs control	1/45	2/33	0.35 (0.03–4.06)	0.403
ten Bokkel Huinink et al,[64] comparison 2	EPO vs control	5/42	2/33	2.10 (0.38–11.56)	0.396
O'Shaughnessy et al[65]	EPO vs control	1/47	0/47	2.53 (0.06–101.35)	0.622
Thatcher et al,[66] comparison 1	EPO vs control	1/42	3/44	0.33 (0.03–3.34)	0.350
Thatcher et al,[66] comparison 2	EPO vs control	5/44	3/44	1.75 (0.39–7.83)	0.463
Fixed-effects model	EPO vs control			1.39 (0.96–2.00)	0.078
Random-effects model	EPO vs control			1.39 (0.96–2.00)	0.078
All trials					
Fixed-effects model	EPO & DARB vs control			1.14 (0.90–1.45)	0.275
Random-effects model	EPO & DARB vs control			1.14 (0.90–1.45)	0.275



OR = odds ratio.

were absent. Recommendations regarding the use of darbepoetin-alfa were also absent. These important guidelines may now be updated to include this new information.

CONCLUSIONS

The studies included in this review comprise the current best evidence on the efficacy and safety profiles of ESPs in the treatment of CIA. No clinically or statistically important differences were found between these products in this setting, especially when used according to their respective product labels. Open-label, community-based studies confirmed ESPs' effectiveness in real-world settings. Existing guidelines should be updated to include recommendations for the use of darbepoetin in the treatment of patients with CIA.

Additional studies should aim to further inform optimal use. For instance, studies that address predictors of response, optimal dosing regimens, and use of iron supplementation would have great clinical impact. The role of ESPs in reducing transfusions and improving QoL in anemic cancer patients not receiving chemotherapy is another area where research is needed.

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Appendix I. Studies that were not included in the review of epoetin and darbepoetin for the treatment of chemotherapy-induced anemia.

Case Reports, Letters, Editorials, Comments, Reviews, and Meta-analyses

Blumberg N, Heal JM. Erythropoietin to treat anaemia in patients with head and neck cancer. *Lancet.* 2004;363:80–81; author reply, 81–82.

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