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Benefits and harms of erythropoiesis-stimulating agents for anemia related to cancer: a meta-analysis

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Abstract

Background: Erythropoiesis-stimulating agents are used to treat anemia in patients with cancer. However, their safety and effectiveness is controversial. We did a systematic review of the clinical efficacy and harms of these agents in adults with anemia related to cancer or chemotherapy.

Methods: We conducted a systematic review of published and unpublished randomized controlled trials (RCTs) using accepted methods for literature searches, article selection, data extraction and quality assessment. We included RCTs involving anemic adults with cancer. We compared the use of erythropoiesis-stimulating agents with nonuse and assessed clinical outcomes (all-cause mortality, cardiovascular events and hypertension, health-related quality of life, blood transfusions and tumour response) and harms (serious adverse events) between groups.

Results: We identified 52 trials (n = 12 006) that met our selection criteria. The pooled all-cause mortality during treatment was significantly higher in the group receiving erythropoiesis-stimulating therapy than in the control group (relative risk [RR] 1.15, 95% confidence interval [CI] 1.03 to 1.29). Compared with no treatment, use of erythropoiesis-stimulating agents led to clinically detectable improvements in disease-specific measures of quality of life. It also reduced the use of blood transfusions (RR 0.64, 95% CI 0.56 to 0.73). However, it led to an increased risk of thrombotic events (RR 1.69, 95% CI 1.27 to 2.24) and serious adverse events (RR 1.16, 95% CI 1.08 to 1.25).

Interpretation: Use of erythropoiesis-stimulating agents in patients with cancer-related anemia improved some disease-specific measures of quality of life and decreased the use of blood transfusions. However, it increased the risk of death and serious adverse events. Our findings suggest that such therapy not be used routinely as an alternative to blood transfusion in patients with anemia related to cancer.

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Anemia related to cancer may be due to the cancer itself or it may be a complication of chemotherapy. Because anemia is associated with adverse clinical outcomes in people with cancer, including impaired quality of life[1] and decreased survival,[2] treatment with erythropoiesis-stimulating agents has been widely used. These agents are costly, and reimbursement policies for their use in patients with cancer-related anemia vary across Canadian jurisdictions. Recent studies suggest that their use in such patients may be associated with an increased risk of adverse events such as thromboembolism.[3] Potential adverse effects have also been identified in patients with chronic kidney disease.[4,5]

Therefore, an assessment of the efficacy and harms of erythropoiesis-stimulating agents in patients with cancer-related anemia would be useful to clinicians, and to jurisdictions that seek to develop an evidence-based reimbursement policy for these drugs. We conducted a systematic review based on work done for the Canadian Agency for Drugs and Technologies in Health[6] to summarize the clinical efficacy and harms of these agents in adults with anemia related to cancer.

Methods

We conducted a systematic review of published and unpublished randomized controlled trials (RCTs) using accepted methods for literature searches, article selection, data extraction and quality assessment and reported our observations in accordance with existing guidelines.[7,8] Full details are published elsewhere.[6]

Literature search

We searched MEDLINE (1950 to Oct. 22, 2007), EMBASE (1988 to Oct. 22, 2007) and all EBM Reviews (Oct. 22, 2007) using exploded terms for erythropoietin, anemia and cancer

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(the search strategy is summarized in Appendix 1, available at www.cmaj.ca/cgi/content/full/cmaj.090470/DC1). We also searched registries of clinical trials, manually searched reference lists of relevant reviews and contacted authors of included studies. The full search strategy is available on request from the authors.[6]

Study selection and validity assessment

We included parallel-group RCTs if they involved adults (18 years or older) with cancer-related anemia and included 30 participants or more in each treatment group; they compared epoetin (alpha or beta) or darbepoetin with a control (no erythropoiesis-stimulating therapy or placebo); and they reported one or more outcomes (all-cause mortality, cardiac event [myocardial infarction, stroke, heart failure or revascularization], hospital admission, quality of life, hypertension, red blood cell transfusions and adverse events). We excluded studies published in a language other than English, French, Spanish or Mandarin.

Two reviewers screened each citation. Trials that were considered to be relevant by any reviewer were retrieved, and the full text was independently assessed by 2 reviewers for inclusion. Disagreements were resolved by a third party through consensus.

We assessed the quality of the studies using characteristics from the Chalmers index[9] as well as other characteristics that may affect the risk of bias.[10–12]

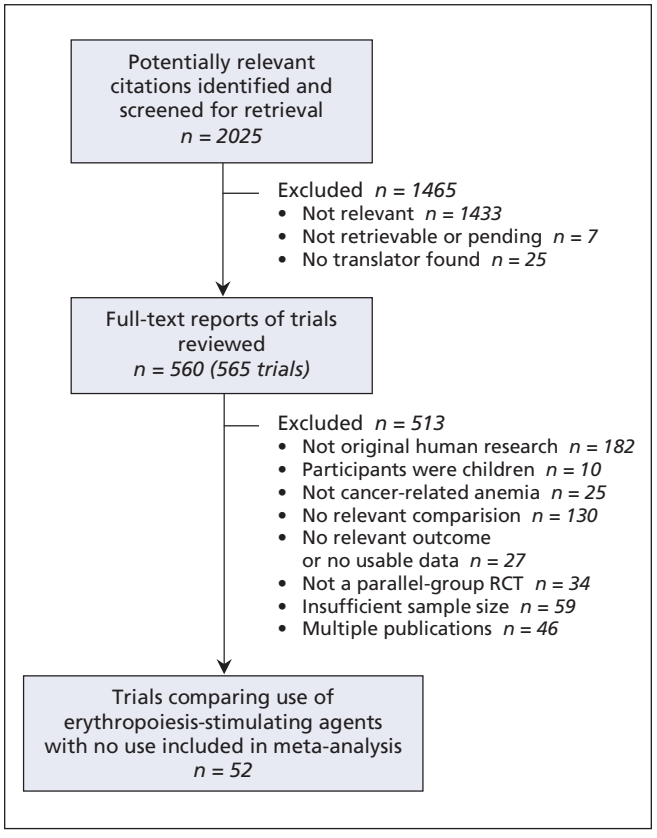

Figure 1: Selection of studies for inclusion in the meta-analysis. RCT = randomized controlled trial.

Data extraction

One reviewer extracted data from the selected trials. A second reviewer checked for accuracy. We preferentially captured intention-to-treat analyses where presented.

We classified adverse events as serious if defined as such by the primary authors or if their severity was unspecified but they led to withdrawal from therapy. Because various quality-of-life measures were reported across studies, we considered only measures that were used in more than one study in each comparison.

Data synthesis and analysis

We pooled results using random-effects models.[13] Because there was no evidence of clinically relevant differences between epoetin and darbepoetin,[6] we refer to these agents collectively as erythropoiesis-stimulating agents. We used the relative risk (RR) and the weighted mean difference to summarize dichotomous and continuous results respectively. We quantified statistical heterogeneity using the I^2 statistic,[14,15] and we used meta-regression analysis[16] to examine whether certain variables influenced the association between therapy and clinical outcome.

In subgroup analyses, we examined the relative risk of clinical outcomes in groups stratified by the baseline hemoglobin level (< 100 g/L, 100–120 g/L, > 120 g/L), by whether participants did or did not receive chemotherapy and by the target hemoglobin level. We defined these strata to correspond to the criteria of the American Society of Clinical Oncology[72] for the use of erythropoiesis-stimulating agents in patients with cancer.

Results

Literature search

We identified 52 eligible trials (n = 12 006) that compared the use of erythropoiesis-stimulating agents with no use (Figure 1).[3,17–65] Forty-two trials (n = 7356) compared the use of epoetin alpha or epoetin beta with no use; 10 trials (n = 4650) compared the use of darbepoetin alpha with no use. Four trials included patients who were undergoing surgery, had preoperative anemia and received perioperative therapy with an erythropoiesis-stimulating agent. The median duration of treatment was 12 (range 2–28) weeks. The median duration of follow-up (stated in 22 studies) was 12 (range 1–37) months. Details of the studies are summarized in Appendices 2 and 3 (available at www.cmaj.ca/cgi/content/full/cmaj.090470/DC1).

Characteristics of participants

Participants with solid tumours were included in 30 trials. Ten trials included only participants with hematologic cancers, and 11 trials included participants with solid tumours and hematologic cancers. One trial did not report the type of cancer among participants, and another included patients with myelodysplastic syndrome. Seven trials reported that no chemotherapy was administered during the study. The median age of study participants was 62 (range 48–71) years. Few trials reported the prevalence of comorbidities among study participants (see Appendices 2 and 3, available at www.cmaj.ca/cgi/content/full/cmaj.090470/DC1).

Methodologic quality

The 52 trials were generally of poor to moderate quality (Appendix 4, available at www.cmaj.ca/cgi/content/full/cmaj.090470/DC1). We found no evidence of publication bias in a weighted regression test[66] in which we used results from analyses comparing all-cause mortality (bias = 0.02, $p = 0.92$).

Outcomes

All-cause mortality

Twenty-eight trials of 31 comparisons ($n = 6525$) reported on all-cause mortality (Figure 2). Mortality was significantly higher among participants in the treatment groups than in the control groups (RR 1.15, 95% confidence interval [CI] 1.03 to 1.29, $I^2 = 0\%$); this corresponded to a risk difference of 2% (risk of death 13% among participants in the control groups). The estimates of treatment effect on mortality were similar when analyses were stratified by agent (RR for epoetin 1.12, 95% CI 0.97 to 1.29, $I^2 = 0\%$; RR for darbepoetin 1.22, 95% CI 1.01 to 1.47, $I^2 = 0\%$). They were also similar when analyses were stratified by type of cancer (RR for solid tumour 1.16, 95% CI 0.99 to 1.37; RR for hematologic cancer 1.11, 95% CI 0.77 to 1.61), were restricted to trials in which the target hemoglobin concentration was 120 g/L or less (RR 1.15, 95% CI 0.94 to 1.40), were restricted to trials with a duration longer than the median of 12 weeks (RR 1.15, 95% CI 0.98 to 1.26) and excluded trials that studied the perioperative administration of erythropoiesis-stimulating agents (RR 1.15, 95% CI 1.02 to 1.28).

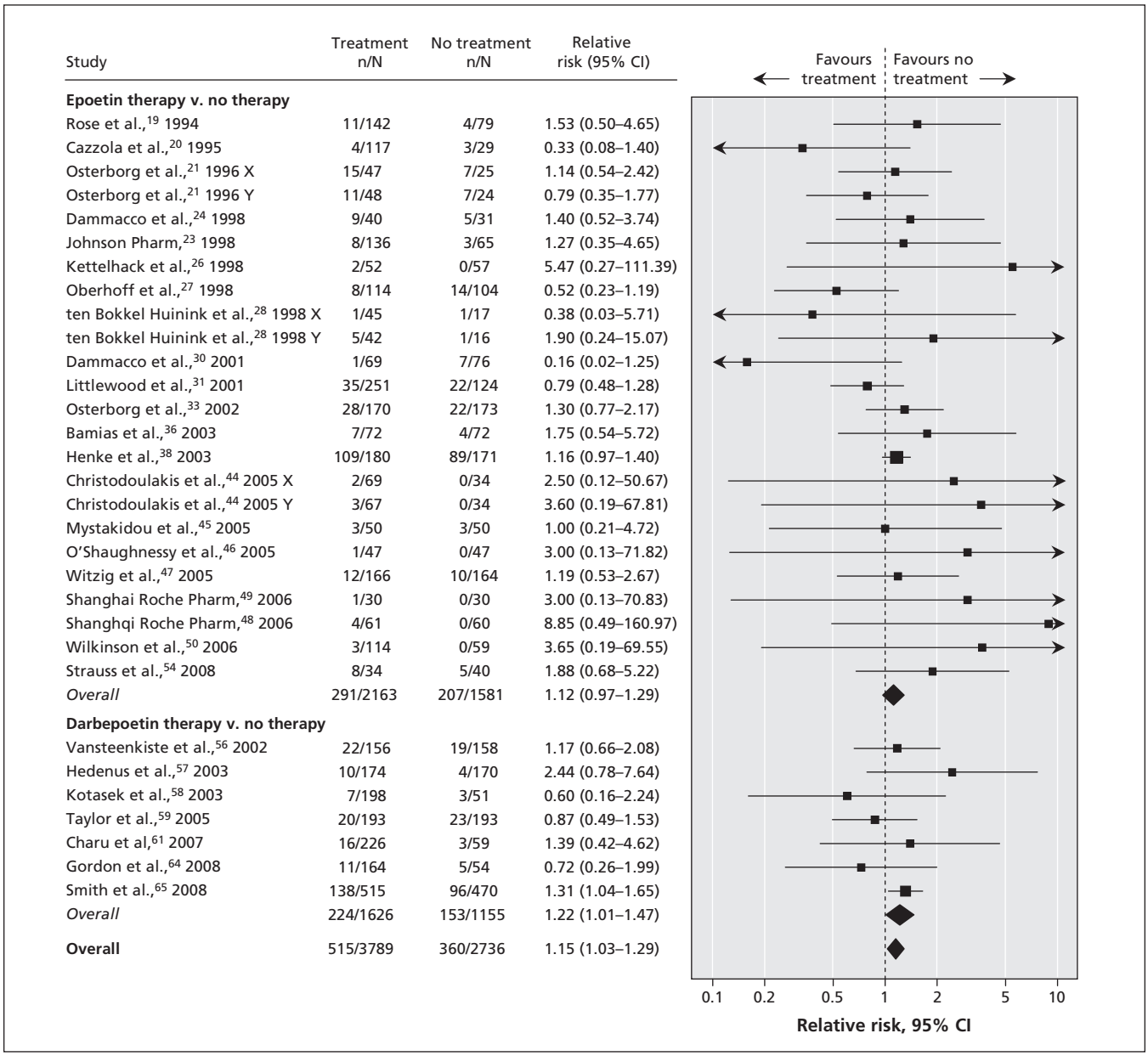

Figure 2: Effect of treatment with erythropoiesis-stimulating agents versus no treatment on all-cause mortality. CI = confidence interval. The letters X and Y following study names are indicated for studies with more than one treatment arm.

None of the variables of interest significantly modified the association between use of erythropoiesis-stimulating agents and mortality in the meta-regression analysis. The potential explanatory variables were duration of treatment, the upper limit of hemoglobin level in the inclusion criteria, the baseline hemoglobin level, use of erythropoiesis-stimulating agents according to the criteria of the American Society of Clinical Oncology, the achieved hemoglobin level, the weekly initial dose of erythropoiesis-stimulating agent, the agent used (epoetin v. darbepoetin), the type of cancer, the use of chemotherapy, the mean age of participants, the percentage of male participants and the characteristics of study quality (all $p > 0.2$ except for study quality, for which $p = 0.13$).

Cardiovascular events and hypertension

Fourteen trials ($n = 3281$) compared the frequency of cardiovascular events between treatment and control groups; 17 trials ($n = 3792$) compared the frequency of hypertension. The pooled risk of these outcomes did not differ significantly between groups (RR for cardiovascular events 1.12, 95% CI 0.83 to 1.50, $I^2 = 0\%$; RR for hypertension 1.41, 95% CI 0.94 to 2.12, $I^2 = 0\%$).

Study	Treatment n	Treatment Mean change (SD)	No treatment n	No treatment Mean change (SD)	Weighted mean difference, random (95% CI)
Change in LASA score					
Littlewood et al,[31] 2001	228	4.80 (26.50)	108	–6.00 (24.60)	10.80 (5.02 to 16.58)
Iconomou et al.,[39] 2003	57	8.00 (19.80)	55	–0.90 (22.80)	8.90 (0.98 to 16.82)
Chang et al.,[43] 2005	166	3.76 (24.30)	169	–6.19 (24.70)	9.95 (4.70 to 15.20)
Mystakidou et al.,[45] 2005	50	32.40 (16.10)	50	4.90 (13.10)	27.50 (21.75 to 33.25)
O'Shaughnessy et al.,[46] 2005	45	–3.60 (24.00)	44	–8.20 (23.50)	4.60 (–5.27 to 14.47)
Savonije et al.,[3] 2005	150	5.30 (24.10)	63	–7.30 (27.80)	12.60 (4.73 to 20.47)
Wilkinson et al.,[50] 2006	91	9.67 (24.00)	50	0.74 (23.50)	8.93 (0.76 to 17.10)
Overall	787		539		12.24 (6.29 to 18.19)
Change in FACT-Anemia (total) score					
Osterborg et al.,[33] 2002	105	14.80 (28.00)	101	8.70 (28.90)	6.10 (–1.67 to 13.87)
Mystakidou et al.,[45] 2005	50	43.30 (18.40)	50	13.40 (14.20)	29.90 (23.46 to 36.34)
Savonije et al.,[3] 2005	155	3.98 (26.80)	65	–3.69 (24.40)	7.67 (0.39 to 14.95)
Overall	310		216		14.66 (–1.09 to 30.41)
Change in FACT-Anemia (general) score					
Littlewood et al.,[31] 2001	194	2.50 (16.00)	88	–3.60 (16.70)	6.10 (1.95 to 10.25)
Osterborg et al.,[33] 2002	106	6.50 (13.80)	103	3.10 (14.40)	3.40 (–0.43 to 7.23)
Savonije et al.,[3] 2005	154	0.90 (10.90)	64	–2.52 (11.00)	3.42 (0.22 to 6.62)
Overall	454		255		4.11 (2.00 to 6.22)
Change in FACT-Fatigue (subscale) score					
Littlewood et al.,[31] 2001	200	3.00 (13.50)	90	–2.20 (12.50)	5.20 (2.01 to 8.39)
Osterborg et al.,[33] 2002	133	5.20 (11.10)	130	3.00 (12.10)	2.20 (–0.61 to 5.01)
Boogaerts et al.,[37] 2003	90	5.39 (12.30)	109	0.41 (8.20)	4.98 (2.01 to 7.95)
Iconomou et al.,[39] 2003	57	4.60 (12.50)	55	–1.00 (12.80)	5.60 (0.91 to 10.29)
Chang et al.,[43] 2005	168	1.55 (11.60)	170	–3.55 (10.70)	5.10 (2.72 to 7.48)
Savonije et al.,[3] 2005	156	3.48 (12.70)	65	–1.67 (11.60)	5.15 (1.70 to 8.60)
Amgen,[60] 2007	298	1.50 (11.80)	298	0.70 (10.27)	0.80 (–0.98 to 2.58)
Charu et al.,[61] 2007	203	6.00 (12.40)	42	2.20 (7.94)	3.80 (0.85 to 6.75)
Gordon et al.,[64] 2008	150	4.80 (11.10)	50	5.00 (11.30)	–0.20 (–3.80 to 3.40)
Smith et al.,[65] 2008	343	–0.02 (11.80)	362	0.52 (10.40)	–0.54 (–2.19 to 1.11)
Overall	1798		1371		3.00 (1.36 to 4.64)
Change in FACT-Anemia (subscale) score					
Littlewood et al.,[31] 2001	200	4.00 (10.50)	90	–2.60 (10.90)	6.60 (3.92 to 9.28)
Osterborg et al.,[33] 2002	133	2.00 (4.30)	130	1.70 (5.20)	0.30 (–0.85 to 1.45)
Boogaerts et al.,[37] 2003	89	0.90 (3.89)	109	–0.11 (3.41)	1.01 (–0.02 to 2.04)
Chang et al.,[43] 2005	168	2.16 (14.70)	170	–4.43 (13.50)	6.59 (3.58 to 9.60)
O'Shaughnessy et al.,[46] 2005	40	–3.00 (11.90)	42	–9.40 (13.80)	6.40 (0.83 to 11.97)
Savonije et al.,[3] 2005	151	3.93 (15.60)	64	–1.91 (14.70)	5.84 (1.46 to 10.22)
Wright et al.,[52] 2007	14	6.50 (14.00)	20	2.60 (14.30)	3.90 (–5.75 to 13.55)
Overall	795		625		3.90 (1.63 to 6.16)
Overall	4144		3006		6.07 (4.39 to 7.74)

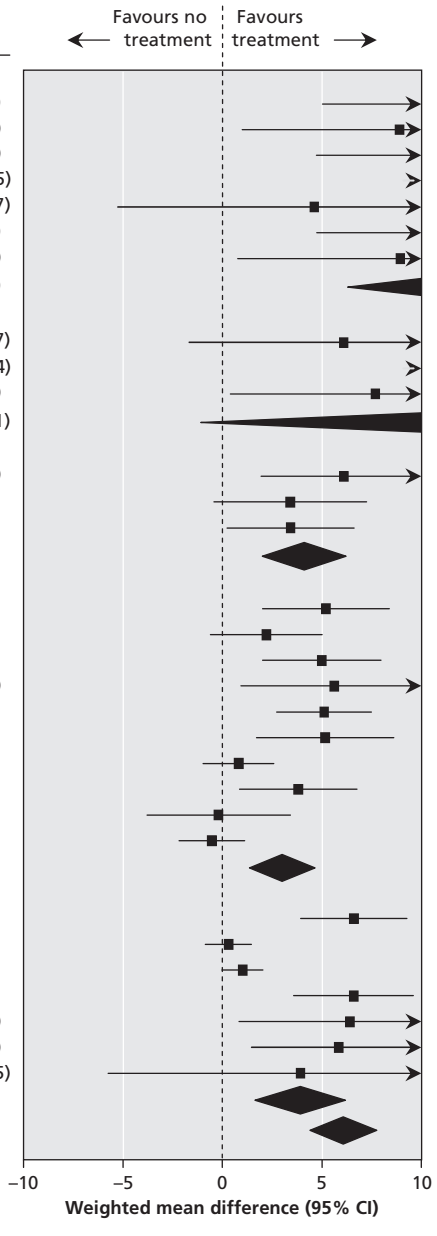

Figure 3: Effect of treatment with erythropoiesis-stimulating agents versus no treatment on change in quality of life. FACT = Functional Assessment of Cancer Therapy, SD = standard deviation, CI = confidence interval.

Health-related quality of life

One otherwise eligible trial reported changes in generic measures of overall quality of life;[37] however, we excluded it because it was the only study that reported these outcomes.

Seven trials (n = 1326) reported changes in disease-specific quality of life using a linear analogue self-assessment (LASA) scale; the changes favoured the use of erythropoiesis-stimulating agents (weighted mean difference 12.24, 95% CI 6.29 to 18.19, I^2 = 81%). Three trials (n = 526) using the Total Functional Assessment of Cancer Therapy–Anemia (FACT-Anemia) scale also reported changes in quality of life that favoured treatment (weighted mean difference 14.66, 95% CI –1.09 to 30.41); I^2 = 93%]. Three other trials (n = 709) using the FACT-General scale reported a change in quality of life that favoured treatment (weighted mean difference 4.11, 95% CI 2.00 to 6.22, I^2 = 0%). Ten trials (n = 3169) reported a significant change in quality of life among recipients of erythropoiesis-stimulating agents, measured using the Fatigue subscale of the FACT-Anemia scale (weighted mean difference 3.00, 95% CI 1.36 to 4.64, I^2 = 73%). For the Anemia subscale of the FACT-Anemia scale, we pooled results from 7 trials (n = 1420) and found a significant improvement in quality of life among participants in the treatment groups (weighted mean difference 3.90, 95% CI 1.63 to 6.16, I^2 = 84%).

All differences in LASA and FACT scores between treatment and control groups met or exceeded the threshold for minimal clinically important differences (Figure 3).[67–71] A previous study estimated that a transfusion of 1 unit of red blood cells (increasing the hemoglobin level by ≥ 10 g/L) results in increases in LASA scores (by mean 9.8), FACT-Anemia Fatigue scores (by mean 4.2) and FACT-General scores (by mean 2.5).[71]

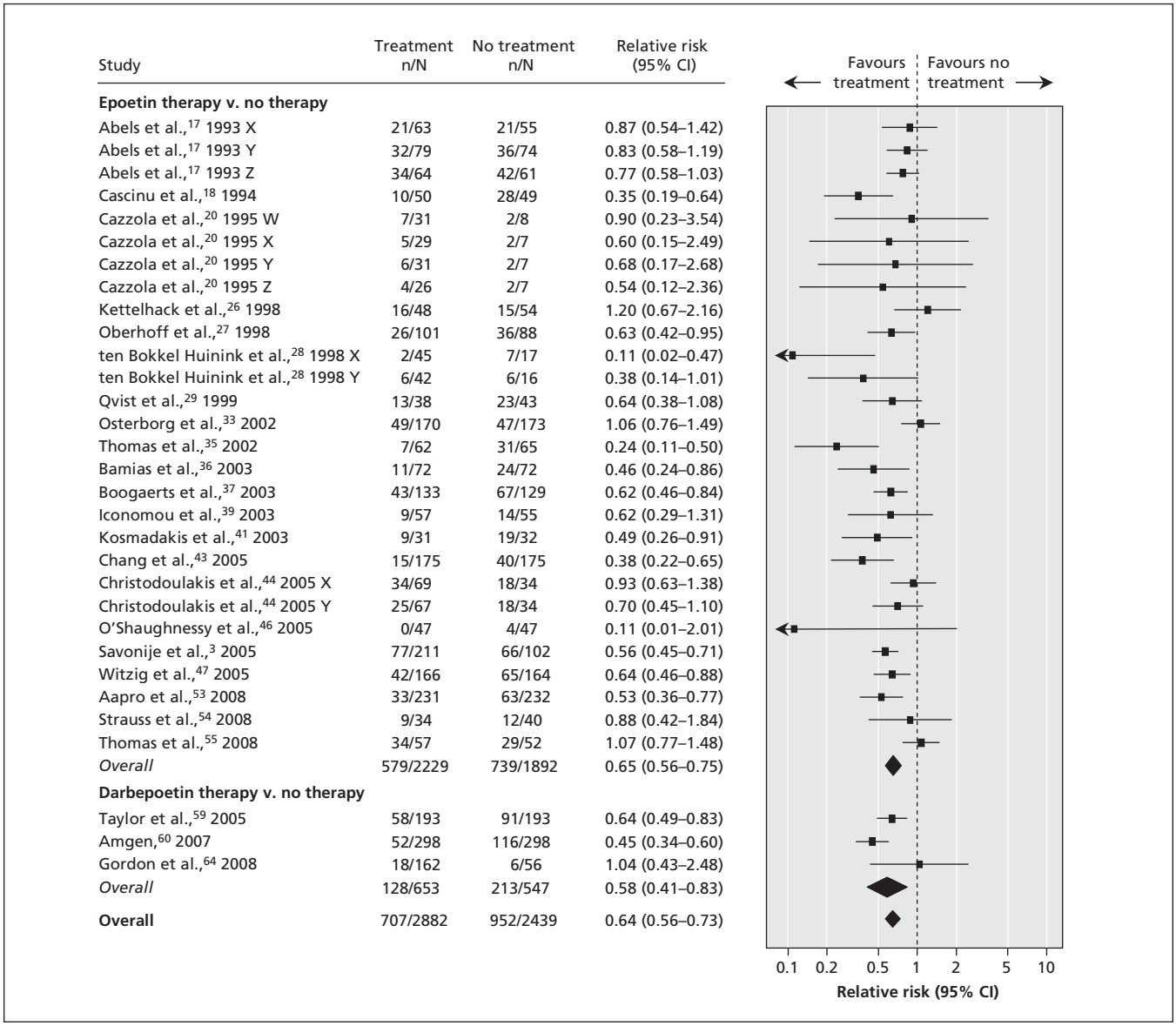

Figure 4: Effect of treatment with erythropoiesis-stimulating agents versus no treatment on blood transfusions. CI = confidence interval. The letters W, X, Y and Z following study names are indicated for studies with more than one treatment arm.

Blood transfusions

Twenty-six trials (n = 5321) compared the proportion of participants who received blood transfusions (Figure 4). The use of erythropoiesis-stimulating agents was associated with a reduction in transfusions (RR 0.64, 95% CI 0.56 to 0.73), which translated to a risk difference of 14% (39% in the control groups). Fifteen trials compared transfusion volume between groups. After pooling the results, we found significantly fewer units of blood transfused among participants in the treatment groups than among those in the control groups (weighted mean difference –0.80 units, 95% CI –0.99 to –0.61); I^2 = 12%]. Although there is no accepted criterion, this likely constitutes a clinically relevant difference. In the meta-regression analysis, we found that none of the variables of interest (same as those for mortality, plus the presence or absence of prespecified criteria for transfusion) significantly modified the association between treatment and transfusion.

Tumour response

Two trials (n = 247) reported the numbers of participants who had complete and partial tumour responses. The numbers did not differ significantly between treatment and control groups (RR for complete response in treatment groups 0.88, 95% CI 0.69 to 1.12, I^2 = 0%; RR for partial response 0.70, 95% CI 0.44 to 1.11, I^2 = 0%).

Adverse events

Twenty-one trials (n = 5891) reported the incidence of adverse events considered by the investigators to be serious. The risk of serious adverse events was significantly higher among recipients of erythropoiesis-stimulating agents than among control patients (RR 1.16, 95% CI 1.08 to 1.25, I^2 = 0%) (Figure 5); this corresponded to a risk difference of 5% (30% among control patients). The results did not change after we excluded the single trial in which adverse events of unspecified severity were considered serious if they led to withdrawal from therapy (RR 1.16, 95% CI 1.08 to 1.24, I^2 = 0%). In the meta-regression analysis, we found that none of the variables of interest (same as those for mortality) significantly modified the association between treatment and serious adverse events.

Thirteen trials of 14 comparisons (n = 3420) reported the frequency of thrombotic events. The risk was significantly higher among patients in the treatment groups than among those in the control groups (RR 1.69, 95% CI 1.27 to 2.24, I^2 = 0%).

Study	Treatment n/N	No treatment n/N	Relative risk (95% CI)
Epoetin therapy v. no therapy			
Abels et al.,[17] 1993 Y	13/81	8/76	1.52 (0.67–3.47)
Cascinu et al.,[18] 1994	0/50	0/49	Not estimable
Rose et al.,[19] 1994	28/142	19/79	0.82 (0.49–1.37)
Cazzola et al.,[20] 1995	15/117	4/29	0.93 (0.33–2.59)
Osterborg et al.,[21] 1996 X	30/47	11/25	1.45 (0.89–2.37)
Osterborg et al.,[21] 1996 Y	24/48	11/24	1.09 (0.65–1.83)
Johnson Pharm et al.,[23] 1998	35/136	19/65	0.88 (0.55–1.41)
Kettelhack et al.,[26] 1998	9/52	8/57	1.23 (0.51–2.96)
Oberhoff et al.,[27] 1998	30/114	29/104	0.94 (0.61–1.46)
ten Bokkel Huinink et al.,[28] 1998 X	9/45	3/17	1.13 (0.35–3.69)
ten Bokkel Huinink et al.,[28] 1998 Y	12/42	2/16	2.29 (0.57–9.10)
Osterborg et al.,[33] 2002	57/170	55/173	1.05 (0.78–1.43)
Boogaerts et al.,[37] 2003	56/133	43/129	1.26 (0.92–1.73)
Henke et al.,[38] 2003	20/180	9/171	2.11 (0.99–4.51)
Witzig et al.,[47] 2005	81/168	73/165	1.09 (0.86–1.37)
Wilkinson et al.,[50] 2006	28/121	9/60	1.54 (0.78–3.06)
Aapro et al.,[53] 2008	97/231	71/231	1.37 (1.07–1.75)
Strauss et al.,[54] 2008	1/34	0/40	3.51 (0.15–83.55)
Overall	545/1911	374/1510	1.17 (1.05–1.30)
Darbepoetin therapy v. no therapy			
Taylor et al.,[59] 2005	83/193	77/193	1.08 (0.85–1.37)
Amgen,[60] 2007	138/298	121/298	1.14 (0.95–1.37)
Charu et al.,[61] 2007 A	66/226	8/59	2.15 (1.10–4.23)
Gordon et al.,[64] 2008	46/164	15/54	1.01 (0.62–1.66)
Smith et al.,[65] 2008	245/515	192/470	1.16 (1.01–1.34)
Overall	578/1396	413/1074	1.15 (1.04–1.27)
Overall	1123/3307	787/2584	1.16 (1.08–1.25)

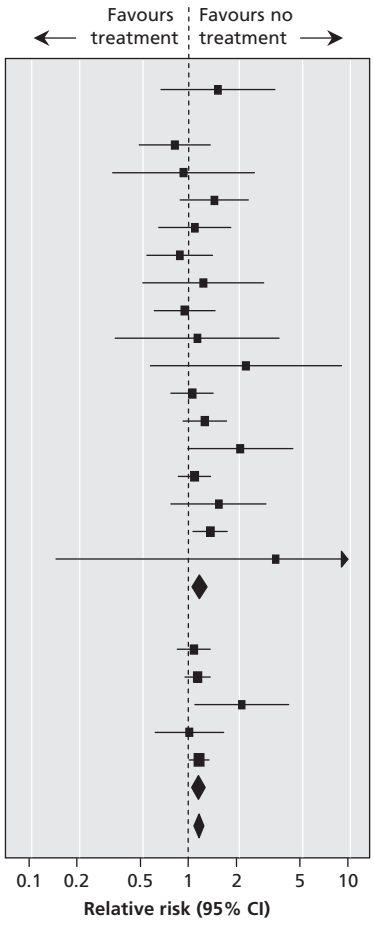

Figure 5: Effect of treatment with erythropoiesis-stimulating agents versus no treatment on serious adverse events. CI = confidence interval. The letters X and Y following study names are indicated for studies with more than one treatment arm.

Subgroup analyses

The quantity of evidence available for analysis declined substantially as the criteria used to define each subgroup became more specific. For example, only 2 studies (3 cohorts) that reported mortality used erythropoiesis-stimulating agents in a fashion that appeared to correspond to all of the criteria of the American Society of Clinical Oncology.

We found little evidence that the clinical benefits or safety of erythropoiesis-stimulating agents in patients defined by the society's criteria differed from the benefits or safety in the total population of cancer patients treated with erythropoiesis-stimulating agents. Specifically, results of the meta-regression analyses comparing the effect of treatment on mortality, serious adverse events, use of blood transfusions and quality of life in subgroups stratified or not stratified according the society's criteria were all nonsignificant ($p \geq 0.25$). The significant increase in serious adverse events and the significant benefits in terms of transfusion prevention and quality of life were observed both in the subgroup stratified according to the society's criteria and in the nonstratified subgroup (Table 1 and Table 2).

Interpretation

We found that the use of erythropoiesis-stimulating agents in cancer patients with anemia resulted in improved scores for several disease-specific measures of quality of life and decreased the use of blood transfusions. The magnitude of improvement in quality of life appeared clinically relevant and was relatively consistent across trials and instruments. However, the use of erythropoiesis-stimulating agents led to an increased risk of all-cause mortality and a significant increase in the risk of serious adverse events. There was no evidence that treatment influenced the risk of cardiovascular events, admission to hospital or tumour response, although there was a borderline increase in the risk of hypertension associated with treatment.

The clinical relevance of the increases in the risk of death and serious adverse events must be considered in the context of the populations studied. Although the relative magnitude of increased risk was modest (15%–16%), the absolute increases in risk were substantial, which reflected the generally adverse underlying prognosis of people with cancer. It is possible, although speculative, that certain patients might choose a reduction in life expectancy in exchange for improved quality of life. However, all of the studies we included were of relatively short duration (median follow-up 12 weeks) and patients were generally aware of the treatment group to which they had been randomly assigned, which may have biased results in favour of treatment with erythropoiesis-stimulating agents.[68] Future studies that address these knowledge gaps are required to determine whether the apparently increased risk of death associated with the use of erythropoiesis-stimulating agents might be offset by improved quality of life.

Current practices for the use of erythropoiesis-stimulating agents in people with cancer-related anemia are more restrictive

Table 1: Effect of therapy with erythropoiesis-stimulating agents on all-cause mortality, use of blood transfusions and incidence of serious adverse events in patients with anemia related to cancer, by baseline hemoglobin level

	Mortality			Blood transfusions			Serious adverse events		
Patient subgroup	n/N	RR (95% CI)	I^2, %	n/N	RR (95% CI)	I^2, %	n/N	RR (95% CI)	I^2, %
Any hemoglobin level at baseline									
All patients	31/6525	1.15 (1.03–1.29)	0	31/5321	0.64 (0.56–0.73)	55	23/5891	1.16 (1.08–1.25)	0
No chemotherapy-induced anemia	8/2252	1.22 (1.06–1.40)	0	7/786	0.80 (0.66–0.98)	5	5/1948	1.30 (1.00–1.68)	32
Chemotherapy-induced anemia	23/4273	1.04 (0.86–1.26)	0	24/4535	0.60 (0.52–0.70)	59	18/3943	1.14 (1.05–1.25)	0
Target hemoglobin < 120 g/L	9/2436	1.15 (0.94–1.40)	2	5/1315	0.55 (0.42–0.73)	47	9/2560	1.18 (1.07–1.31)	0
Baseline hemoglobin < 100 g/L									
All patients	14/3631	1.04 (0.81–1.32)	28	16/1765	0.72 (0.62–0.84)	22	11/2908	1.13 (1.03–1.25)	0
Chemotherapy-induced anemia	13/2646	0.96 (0.73–1.26)	18	11/1647	0.71 (0.60–0.83)	26	10/1923	1.11 (0.97–1.26)	0
Chemotherapy-induced anemia, target hemoglobin < 120 g/L	3/289	0.77 (0.36–1.66)	41	2/361	0.50 (0.29–0.87)	65	4/505	1.27 (1.00–1.60)	0
Baseline hemoglobin 100–120 g/L	14/2478	1.16 (0.99–1.36)	0	12/3272	0.57 (0.47–0.69)	56	11/2782	1.22 (1.09–1.37)	0
Baseline hemoglobin > 120 g/L	1/94	3.00 (0.13–71.82)	NA	2/175	0.46 (0.11–1.88)	34	No studies	–	–
Baseline hemoglobin unclear	2/322	2.20 (0.38–12.79)	34	1/109	1.07 (0.78–1.48)	NA	1/201	0.88 (0.55–1.41)	NA

Note: RR = relative risk, CI = confidence interval, NA = not applicable.

Table 2: Effect of therapy with erythropoiesis-stimulating agents on health-related quality of life in patients with anemia related to cancer, by baseline hemoglobin level

	Measure of quality of life								
	LASA scale			FACT-Fatigue subscale			FACT-Anemia subscale		
Patient subgroup	n/N	RR (95% CI)	I^2, %	n/N	RR (95% CI)	I^2, %	n/N	RR (95% CI)	I^2, %
Any hemoglobin level at baseline									
All patients	7/1326	12.24 (6.29 to 8.19)	81	10/3169	3.00 (1.36 to 4.64)	73	7/1420	3.90 (1.63 to 6.16)	84
No chemotherapy-induced anemia	1/100	27.50 (21.75 to 33.25)	NA	3/1150	0.92 (–1.85 to 3.69)	69	No studies	–	–
Chemotherapy-induced anemia	6/1226	9.80 (6.95 to 12.64)	0	7/2019	3.87 (2.16 to 5.57)	60	7/1420	3.90 (1.63 to 6.16)	84
Target hemoglobin < 120 g/L	3/576	15.59 (3.26 to 27.92)	91	5/1687	2.61 (–0.12 to 5.34)	82	2/536	3.61 (–1.84 to 9.07)	92
Baseline hemoglobin < 100 g/L									
All patients	1/336	10.80 (5.02 to 16.58)	NA	4/1457	2.78 (–0.25 to 5.80)	82	3/751	2.26 (–0.22 to 4.73)	89
Chemotherapy-induced anemia	1/336	10.80 (5.02 to 16.58)	NA	3/752	4.03 (2.09 to 5.97)	21	3/751	2.26 (–0.22 to 4.73)	89
Chemotherapy-induced anemia, target hemoglobin < 120 g/L	No studies	–	–	1/199	4.98 (2.01 to 4.65)	NA	1/198	1.01 (–0.02 to 2.04)	NA
Baseline hemoglobin 100–120 g/L	5/901	13.77 (5.95 to 21.59)	85	6/1712	3.21 (1.16 to 5.26)	66	3/587	6.20 (3.80 to 8.60)	0
Baseline hemoglobin > 120 g/L	1/89	4.60 (–5.27 to 14.47)	NA	No studies	–	–	1/82	6.40 (0.83 to 11.97)	NA
Baseline hemoglobin unclear	No studies	–	–	No studies	–	–	No studies	–	–

Note: CI = confidence interval, FACT = Functional Assessment of Cancer Therapy, LASA = linear analogue self-assessment, NA = not applicable, RR = relative risk.

than they once were. Guidelines from the American Society of Clinical Oncology[72] indicate that the agents should not be used unless patients are receiving concurrent chemotherapy; however, they cautiously recommend their use when the hemoglobin level is less than or approaching 100 g/L (or 100–120 g/L in certain circumstances, including decreased cardiopulmonary reserve). The recently revised Health Canada label for darbepoetin is similar to the society's criteria: it indicates that the agent should be used for cancer-related anemia under very specific conditions: the presence of nonmyeloid cancer; anemia due to chemotherapy; a hemoglobin level less than 100 g/L; and a target hemoglobin level of no more than 120 g/L. Although we identified 2 studies that reported mortality and met the last 3 conditions (and were therefore consistent with the American Society of Clinical Oncology's criteria), both enrolled patients with a form of myeloid cancer (multiple myeloma). Therefore, none of the studies that reported mortality used erythropoiesis-stimulating agents in a manner consistent with the current Health Canada label for darbepoetin. The Health Canada label for epoetin is similar to the label for darbepoetin; however, it is slightly less restrictive because it does not specify the hemoglobin level at which therapy should be initiated.

There is a striking lack of data to support Health Canada's labels and the American Society of Clinical Oncology's guidelines for the use of erythropoiesis-stimulating agents in people with cancer-related anemia. Although it is rational to restrict the use of a potentially harmful therapy, it is unclear whether following the directions in the current label permits the identification of patients with more favourable risk–benefit ratios. In particular, the fact that the risk of death was not significantly increased in the subgroup of trials in which participants met the American Society of Clinical Oncology's criteria does not allay the safety concerns raised by the primary analysis.[73,74] We found no evidence that the risks or benefits of treatment differed between patients who did or did not receive chemotherapy, or who did or did not meet the society's criteria. This suggests that the most reliable estimates of benefit and harm in these subgroups are likely to be the pooled estimates obtained by combining results from all available trials.[73,75] These findings suggest that erythropoiesis-stimulating agents should not be routinely used as an alternative to blood transfusion in patients with chemotherapy-induced anemia unless future studies document safety and clinical benefits in this population.

Strengths and limitations

Our study was an up-to-date, comprehensive systematic review of the clinical implications of use of erythropoiesis-stimulating agents for cancer-related anemia. We specifically

addressed the potential clinical benefits of these agents when used according to current clinical practice guidelines. The studies we included were conducted on several continents over the last decade; enrolled more than 12 000 participants in total; involved 3 types of agents (epoetin alpha, epoetin beta and darbepoetin alpha); and focused on people with different types of cancer. Participants in randomized controlled trials tend to be less likely to experience adverse events and more likely to benefit from experimental therapies than unselected individuals with the same diseases. Despite this, the results of our review are likely to be externally valid.

Our study had limitations. Although we reduced the potential for bias by following recommendations for systematic reviews, the methodologic quality of the studies we included was poor to moderate. Also, many of the studies did not specify criteria for administering blood transfusions, which may have reduced internal validity. Second, we excluded studies with fewer than 30 participants; however, this unlikely influenced our conclusions, because the number of participants in the included trials was large. Third, the clinical effects of erythropoiesis-stimulating agents appeared to be homogeneous in the meta-regression analysis; however, this technique has limitations, including low statistical power and the ecological fallacy.[76] Therefore, the risk–benefit ratio of erythropoiesis-stimulating agents in cancer-related anemia may vary in certain clinical populations.

Conclusion

Use of erythropoiesis-stimulating agents in patients with cancer-related anemia improved disease-specific measures of quality of life and decreased the use of blood transfusions. However, use of the agents led to an increased risk of all-cause mortality and serious adverse events. We found no evidence that the risks or benefits of treatment differed among patients who did or did not meet recently revised criteria for the use of these agents in patients with cancer. Our findings suggest that existing practice guidelines should be revised to recommend against the routine use of erythropoiesis-stimulating agents as an alternative to blood transfusion in patients with anemia related to cancer.

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