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ORIGINAL ARTICLE

The use of erythropoiesis-stimulating agents in patients with non-myeloid hematological malignancies: a systematic review

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Abstract The effectiveness of erythropoiesis-stimulating agents (ESAs) for the treatment of anemia in patients with non-myeloid hematological malignancies needs to be assessed as the response to their administration is not uniform and their cost is high. We conducted a systematic review (SR) of the literature to identify reports of the effect of ESAs on survival, quality of life (QOL), transfusion requirements, and anemia. The entries to MEDLINE, EMBASE, and the Cochrane Library databases, and abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology and the American Society of Hematology were searched. Seventeen reports and five abstracts of randomized trials fulfilled prospective criteria for inclusion. Five trials reported on survival; three failed to detect differences between groups and two demonstrated inferior survival in patients allocated to an ESA. Seven trials and three abstracts reported on QOL with four articles and three abstracts describing improvements in patients allocated to erythropoietin. However, important methodologic limitations were identified in these reports. Seven randomized controlled trials reported a reduction in the proportion of patients transfused. The absolute risk reduction in transfusions ranged from 15% to 24%. This is the only SR that assesses the use of erythropoiesis-stimulating agents specifically in patients with hematological malignancies. We conclude that available data evaluating ESAs in patients with hematologic malignancies demonstrate that these agents reduce transfusion requirements. Limitations of these data preclude conclusions that these agents improve QOL. More data are required to confirm the inferior survival associated with ESAs.

Keywords Erythropoietin · Darbepoetin · Erythropoiesis-stimulating agents · ESAs · Lymphoproliferative disorders · Multiple myeloma · Hematological malignancies

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Introduction

Anemia is a common occurrence in patients with non-myeloid hematological malignancies (i.e., multiple myeloma, non-Hodgkin's lymphoma, chronic lymphocytic leukemia, Hodgkin lymphoma). At diagnosis, 62% of patients with

multiple myeloma have anemia and 8% will have a hemoglobin level less than 80 g/L [1]. In lymphoma, 32% of patients will have anemia when they are first diagnosed [2], and an estimated 37% to 100% of patients treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy will develop anemia during the course of their therapy [3, 4]. Overall, 45% to 90% of patients with multiple myeloma and non-Hodgkin's lymphoma receiving chemotherapy will require a transfusion [5–7].

Erythropoiesis-stimulating agents are effective agents to treat anemia [5–7] and are not associated with the adverse reactions of red cell transfusions (i.e., viral transmission, allergic reactions, hemolytic transfusion reactions, bacterial contamination, and transfusion-related acute lung injury) [8]. Although transfusion-associated complications are infrequent, the Commission of Inquiry into the Blood System in Canada [9] recommended the use of available alternatives to blood transfusion. Erythropoiesis-stimulating agents are costly and balancing their effectiveness and toxicities against their cost needs to be assessed to ensure that further constraints are not placed on the health care system. Systematic reviews, such as the report by the Cochrane Collaboration [10] and practice guidelines such as the guideline prepared by the American Society of Hematology and the American Society of Clinical Oncology [11], have been previously conducted for patients with all cancers but this is the first systematic review that addresses hematological malignancies specifically.

The purpose of this review is to update our previous systematic review of the literature (available at: http://www.cancercare.on.ca/pdf/pebc6-12f.pdf) to determine whether erythropoiesis-stimulating agents should be recommended for patients with non-myeloid hematological malignancies. This systematic review was used to develop a clinical practice guideline by the Hematology Disease Site Group of Cancer Care Ontario's Program in Evidence Based Care.

Materials and methods

A systematic search was conducted of the databases MEDLINE and EMBASE for articles published from 1966 to March 2008 and of the Cochrane Library (2008, Issue 1). Citations containing the following medical subject heading terms "non-myeloid hematological malignancies", "lymphoma", "multiple myeloma", "chronic lymphocytic leukemia", combined with each of the following search terms "erythropoietin", "epogen", "epo", "epoetin", "eprex", "darbepoetin alpha", and subsequently with "practice guidelines", "meta-analyses", "systematic reviews", "quantitative review", "methodological review", "randomized controlled trial", and "controlled clinical trial" were retrieved. Conference proceedings from the American Society of Clinical Oncology (1996 to 2007) and the American Society of Hematology (1996 to 2007) and reference lists were also searched. The search began from the year 1985, as this was when human erythropoietin was first cloned [12].

A study was included in the systematic review if it adhered to the following criteria: (1) The study was a randomized controlled trial involving the use of either erythropoietin or darbepoetin alpha as an intervention in patients with lymphoma, multiple myeloma, chronic lymphocytic leukemia, and/or Hodgkin lymphoma, and (2) it included one of the following primary outcome measures: survival, transfusion requirements, quality of life, or correction/improvement of anemia. We excluded reports if: (1) they were non-randomized, phase I or phase II trials; (2) hematological patients could not be differentiated from patients with solid tumors; (3) they included patients with acquired immunodeficiency syndrome-associated lymphoma; (4) they focused solely on patients with multiple myeloma with renal failure requiring hemodialysis; (5) they included patients having peripheral blood stem cell transplants; (6) they were published in a language other than English; or (7) they were letters and editorials.

Two reviewers (NS, RM) independently assessed the citations for inclusion/exclusion criteria. When a discrepancy occurred between the reviewers, the full publication was retrieved. Two reviewers (NS, AH) analyzed the manuscripts.

Standardized data abstraction forms were used to abstract information on author, year of publication, and study characteristics. Study characteristics abstracted included year of study, the number of centers involved, characteristics of participants, inclusion and exclusion criteria, study design, sampling methods, appropriateness of randomization technique, sample size, intervention, co-interventions (i.e., iron), hemoglobin concentrations for transfusion, length of follow-up, survival, quality of life, the proportion of patients transfused, predefined assessment of adverse events, adverse events, and handling of withdrawals. We evaluated the quality of the studies based on whether (1) the groups included were comparable, (2) a hemoglobin concentration for transfusion was specified, (3) there was a blinded outcome assessment, (4) confounding factors were present or considered, (5) the sample size was predetermined, (5) an intention-to-treat analysis was conducted, and (6) whether there was adequate follow-up and handling of missing data.

We described the hemoglobin criteria used for study entry and the outcomes of the proportion of patients transfused, quality of life, performance status, and the hemoglobin or hematocrit increment. Although anemia was

an outcome measure in many of the identified trials, it was considered an intermediate outcome and only of significance if a change in hemoglobin affected survival, transfusion requirements, or quality of life.

Pooling

The parameters considered for pooling were the increment in the level of hemoglobin, the proportion of patients transfused, transfusion requirements, survival, quality of life, and adverse events. The reporting of these parameters was inconsistent among the trials. Several trials reported on these outcomes, but different inclusion criteria, hemoglobin concentrations used for transfusion, dosing regimens, duration of assessments, and the use of co-interventions were used. In addition, there were methodological limitations in the assessment of quality of life of patients. Due to the variation in reporting and limitations in assessment of survival and quality of life, pooling of data was not conducted on any of the outcomes.

Number needed to treat

For studies showing a reduction in the proportion of patients transfused or an improvement in quality of life, the number needed to treat to prevent one transfusion or to improve the quality of life in one patient was calculated as the reciprocal of the absolute risk reduction.

For this report, erythropoietin will be used to denote epoetin alpha and beta, and erythropoiesis-stimulating agents to denote epoetin and darbepoetin.

Results

Results of the literature search

Seventeen published reports [5–7, 13–26] and five abstracts [27–31] formed the basis for this systematic review. Two abstracts are included concurrently as they represent the same data [28, 29]. The characteristics of the studies and results are illustrated in Tables 1 and 2. Two studies [21, 22] are not included in the tables. One of these [22] reported the survival of a cohort of patients previously reported in another publication [15], and the other [21] was a pooled analysis of four randomized controlled trials. One additional report [32] included survival data on a previous publication [21].

Quality of the studies

Table 1 illustrates the characteristics of the studies. The hemoglobin concentration for transfusion ranged from 70 g/L to 100 g/L. Seven published trials [7, 13–17, 26] and one preliminary study in abstract form [28] were double-blinded and placebo-controlled. Seven studies reported sample size calculations that were adequately powered [13, 15, 19, 23–26]. One of the studies was powered to detect a difference in quality of life [25], but there were no studies powered to detect a difference in survival. Six trials and four abstracts did not analyze their data based on an intention-to-treat analysis [6, 17, 18, 20, 24, 26–28, 30, 31]. All of the fully published trials reported on the number of patients who completed the trials. Eight studies assessed quality of life using validated instruments [7, 13, 15, 16, 24–27]. The reports did not provide baseline values of quality of life scores, did not report the proportion of patients who improved, and did not provide clinical correlations with the changes in quality of life parameters. Two studies detailed methods of adjusting for missing data [25, 26].

Table 2 describes the results of the trials. Four trials and one abstract evaluated patients solely with multiple myeloma [5, 7, 17, 18, 30]; three trials evaluated patients with solid tumors and non-myeloid hematological malignancies [16, 24, 26]; seven trials and one abstract evaluated patients with multiple myeloma, lymphoma, and chronic lymphocytic leukemia [6, 13–15, 19, 23, 25, 27]; one trial evaluated patients with diffuse large B cell lymphoma [31]; and one trial and two abstracts evaluated only patients with chronic lymphocytic leukemia (Table 2) [20, 28, 29]. The majority of patients were receiving chemotherapy at the time of treatment with erythropoietin. Only one trial evaluated patients not receiving chemotherapy [26]

Three trials and one abstract [13, 14, 26, 31] reported on the use of darbepoetin alfa and the remaining trials reported on the use of erythropoietin.

Outcomes

Survival

Two reports assessed survival in patients treated with erythropoietin [16, 22], and three [21, 26, 31] assessed survival in patients treated with darbepoetin alpha. The first [16], a double-blind, randomized, placebo-controlled trial of 375 patients with solid or non-myeloid hematological malignancies, did not show a statistical difference in overall survival. At 12 months of therapy, estimated overall survival was 52% for patients with hematological malignancies treated with erythropoietin and 40% for patients treated with placebo (the p value was not reported) [16]. The second report [22] was a follow-up study of an earlier published double-blind randomized trial of transfusion-dependent patients with lymphoproliferative disorders treated with epoetin beta or placebo [15]. The minimum length of follow-up was 17.5 months. There was no

Table 1 Characteristics of randomized controlled trials of erythropoietin and darbepoetin in non-myeloid hematological malignancies

Authors, year (reference)	Comparable groups	Transfusion threshold (g/L)	Double blinded?	Duration of assessment (weeks)	Confounding[a]	Power	Intention-to-treat	Adequate follow-up
Darbepoetin alpha								
Smith et al., 2007 [26]	Yes	NR	Yes	16	Patients with various malignancies	90% power to detect a 40% difference in the incidence of transfusion (20% placebo, 12% DAR)	No	52% completed the 16-week study
Hedenus et al., 2003 [13]	Yes	≤80[b]	Yes	16	No	90% to detect an increase in Hb from 25% to 50%	Yes	84% completed the study, 84% completed the QOL scale
Hedenus et al., 2002 [14]	Yes	≤80	Yes	16	No	NR	Yes	95% completed the study
Erythropoietin								
Straus et al., 2006 [25]	Yes	NR	No	16	No	80% to detect a 3-point difference in FACT-An	Yes	86% completed the QOL scale
Morishima et al., 2006 [24]	Yes	None	Yes	12	Patients with lung cancer and lymphoma	90% to detect a change in Hb of 20 g/L between the 9,000- and 36,000-IU groups	No	80% included in the efficacy analysis
Cazzola et al., 2003 [23]	Yes	≤85	No	16	No	80% to determine non-inferiority in time-adjusted Hb area under the curve between weeks 5 and 16	Yes	91% completed the study
Österborg et al., 2002 [15]	Yes	<85[c]	Yes	16	No	80% to detect a difference in transfusion-free survival from 25% to 50% in the subgroups	Yes	82% completed the study
Littlewood et al., 2001 [16]	Yes	<80[b]	Yes	36	Patients with various malignancies included	NR	Yes	58% completed the study, 7% excluded from QOL
Dammacco et al., 2001 [7]	Yes	≤80	Yes	12	No	NR	Yes	86% completed the study
Dammacco et al., 1998 [5]	Yes	<70	No	24	No	NR	Yes	69% completed the study
Österborg et al., 1996 [6]	Yes	<100	No	24	No	NR	No	84% completed the study
Cazzola et al., 1995 [19]	Yes	NR	No	8	No	80% to detect a weekly Hb increase between control and each group	Yes	90.4% completed the study
Garton et al., 1995 [17]	Yes	NR	Yes	12	No	NR	No	83% completed the study
Pangalis et al., 1995 [20]	NR	NR	No	12	Vague patient selection criteria	NR	No	100% completed the study
Silvestris et al., 1995 [18]	NR	NR	No	24	No	NR	No	93% completed the study
Abstracts								
Delarue et al., 2006 [31]	NR	≤90	No	52	Unable to assess	NR	NR	NR
Rubio-Martinez et al., 2003 [30]	NR	<90	No	8	Unable to assess	NR	No	70% have completed the study to date (preliminary report)
Straus et al., 2002 [27]	NR	NR	No	16	Unable to assess	NR	No	NR
Rose et al., 1994 [28]; Rai et al., 1995 [29]	Yes	NR	Yes	12	Unable to assess	NR	No	NR

Hb Hemoglobin, *QOL* quality of life, *NR* not reported

[a] Confounding occurs when a third factor is related both to a risk factor and an outcome which can bias the association of the factor and the outcome.

[b] Based on physician discretion, but ≤80 g/L recommended

[c] Or medically indicated

Table 2 Results of the randomized controlled trials of erythropoietin and darbepoetin in non-myeloid hematological malignancies

Authors, year (reference)	Patient eligibility	Erythropoietin/darbepoetin treatment regimen	*N*	Hb/Hct increment	Outcome	Primary /secondary outcome	Result
Darbepoetin alpha							
Smith et al., 2007 [26]	MM, NHL, CLL, HL, solid tumors Hb ≤110 g/L	DAR 6.75 μg/kg/4 weeks	517	7.3 g/L	No. of transfusion	Primary	176 vs. 215 (p=0.3)
		Placebo	470	2.9 g/L (p<0.01)	QOL	Secondary	No difference
					Performance status	NR	
Hedenus et al., 2003 [13]	MM, NHL, HL, CLL Hb ≤110 g/L	DAR 2.25 μg/kg 1×/week + CT	174	60%[a,b]	Proportion transfused	Secondary	31% vs. 48% (p<0.001)
		Placebo + CT	170	18%[a,b] (p<0.0001)	QOL	Secondary	Improvement (p=0.032)
					Performance status	NR	NR
Hedenus et al., 2002 [14]	MM, NHL, HL, CLL Hb ≤110 g/L	DAR 1.0 μg/kg 1×/week + CT	11	45%[a,b]	Proportion transfused	Secondary	27% vs. 27% vs. 15% vs. 45% (p=ns for DAR vs. placebo)
		DAR 2.25 μg/kg 1×/week + CT	22	55%[a,b]			
		DAR 4.5 μg/kg 1×/week + CT	22	62%[a,b]	QOL	NR	NR
		Placebo + CT	11	10%[a,b] (p<0.01 DAR vs. placebo)	Performance status	NR	NR
Erythropoietin							
Straus et al., 2006 [25]	NHL, HL, CLL, MM Hb 100–120 g/L	EPO-α 40,000 IU/week + CT	135	12 g/L	Proportion transfused	Secondary	17.8% vs. 26.1%, p=0.11
		EPO-α 40,000/week when Hb <90 g/L + CT	134	2 g/L (p<0.0001)	QOL	Primary	Improvement (p=0.03)
					Performance status	NR	
Morishima et al., 2006 [24]	LYM, Lung Hb ≤110 g/L	EPO-β 9,000 IU/week + CT	22	0 g/L[a]	Proportion transfused	Secondary	22.7% vs. 16.7% vs. 0 (p=0.02)
		EPO-β-18,000 IU/week +CT	24	10 g/L[a]	QOL	Secondary	No difference
		EPO-β 36,000 IU/week + CT	23	15 g/L (p<0.05 for 9,000 vs. 36,000)	Performance status	NR	
Cazzola et al., 2003 [23]	NHL, CLL, MM Hb 90 to 110 g/L	EPO-β 30,000 IU 1×/week + CT	119	24 g/L[a]	Proportion transfused	Secondary	9% vs. 14% (p=0.14)
		EPO-β 10,000 IU 3×/week + CT	122	23 g/L[a]	QOL	NR	NR
					Performance status	NR	NR
Österborg et al., 2002 [15]	MM, NHL, CLL Hb <100 g/L	EPO-β 150 U/kg 3×/week + CT	170	67%[b]	Proportion transfused	Primary	33.3% vs. 52.4% (p=0.0012)
		Placebo + CT	173	27%[b] (p<0.0001)	QOL	Secondary	Improvement (p<0.05)
					Performance status	NR	NR
Littlewood et al., 2001 [16]	MM, NHL, HL, CLL, solid tumors Hb ≤105 g/L	EPO-α 150 U/kg 3×/week + CT + Fe	251	22 g/L[c]	Proportion transfused	Primary	24.7% vs. 39.5% (p=0.0057)
		Placebo + CT	124	5 g/L[c] (p<0.001)	QOL	Secondary	Improvement (p=0.0002)
					Performance status	NR	NR
Dammacco et al., 2001 [7]	MM Hb <110 g/L	EPO-α 150 U/kg 3×/week + CT	69	18±20.5 g/L[c]	Proportion transfused	Primary	27.5% vs. 47.4% (p=0.02)
		Placebo + CT	76	0.0±11.8 g/L[c] (p<0.001)	QOL	Secondary	No improvement
					Performance status	Secondary	Mean change from baseline favored EPO-α (p=0.038)
Dammacco et al., 1998 [5]	MM Hb <100 g/L	EPO-α 150 U/kg 3×/week	40	20.9±17 g/L[c,d]	Proportion transfused	Primary	25%[e] vs. 45%[e] (p=0.23)
		Control CT—86% of pts	31	−1.7±15 g/L[c,d] (p<0.0001)	QOL	NR	NR
					Performance status	Secondary	Deteriorated in control group (p=0.03)

Table 2 (continued)

Authors, year (reference)	Patient eligibility	Erythropoietin/darbepoetin treatment regimen	*N*	Hb/Hct increment	Outcome	Primary /secondary outcome	Result
Österborg et al., 1996 [6]	MM, NHL, CLL	EPO-β 10,000 U/day	47	21 g/L[e,f]	Proportion transfused	Primary	58%[g] vs. 64%[g] vs. 82%[g] ($p<0.05$)
	Hb <100 g/L	EPO-β 2,000 U/day (titrated)	48	15 g/L[e,f]			NR
		Control	49	5 g/L[e,f]	QOL	NR	NR
		CT—88% of pts		(p=ns)	Performance status	NR	
Cazzola et al., 1995 [19]	MM, NHL, CLL	EPO-β 1,000 U/day	31	−0.4 g/L[g] (p=0.5702)	Proportion transfused	Secondary	23% vs. 17% vs. 19% vs. 15% vs. 28% (p=ns)
	Hb ≤110 g/L	EPO-β 2,000 U/day	29	2.2 g/L[g] (p=0.0553)			
		EPO-β 5,000 U/day	31	4.3 g/L[g] (p=0.0140)	QOL	NR	NR
		EPO-β 10,000 U/day	26	5.8 g/L[g] (p=0.0001)	Performance status	NR	NR
		Control	29	0.4 g/L[g]			
		CT—79% of pts					
Garton et al., 1995 [17]	MM	EPO-α 150 U/kg 3×/week + CT	11	Significant difference in mean slopes, EPO vs. placebo (p=0.02)	Proportion transfused	NR	NR
	Hct ≤0.3	Placebo + CT	13		QOL	NR	NR
					Performance status	NR	NR
Pangalis et al., 1995 [20]	CLL	EPO-α 150 U/kg 3×/week + CT	6	NR	Proportion transfused	NR	NR
	Hct <0.32	Placebo + CT	3	NR	QOL	NR	NR
					Performance status	NR	NR
Silvestris et al., 1995 [18]	MM	EPO-α 150 U/kg 3×/week + CT + Fe	30	20 g/L	Proportion transfused	NR	NR
	Hb ≤80 g/L	Control + CT	24	NR	QOL	NR	NR
					Performance status	NR	NR
Abstracts							
Delarue et al., 2006 [31]	DLBCL	DAR 2.25 μg/kg/week + CT	63	120 g/L[h]	Proportion transfused	NR	29% vs. 55% (p=0.01)
		CT + transfusion and EPO/DAR if Hb ≤90 g/L	67	106 g/L[h]	QOL	NR	NR
					Performance status	NR	NR
Rubio-Martinez et al., 2003 [30]	MM	EPO-α 10,000 U 3×/week	46	77%[i]	Proportion transfused	NR	NR vs. 38%
	Hb: males <120 g/L, females <110 g/L	Control	45	NR[i]	QOL	NR	Better in EPO group (p=NR)
					Performance status	NR	NR
Straus et al., 2002 [27]	MM, CLL, lymphoma	EPO-α 40,000 U/week + CT	77	8.0±25 g/L	Proportion transfused	NR	NR
	Hb 100–120 g/L	Control + CT	102	−8.0±1 g/L (p=0.005)	QOL	NR	Improvement ($p<0.05$)
					Performance status	NR	NR
Rose et al., 1994 [28]	CLL	EPO-α 150 U/kg 3×/week	141	5.7%[j]	Proportion transfused	NR	NR

Rai et al., 1995 [29]	Hct <32%	Placebo	81	1.5[j]	QOL	Secondary		Improved energy, self-rated health, physical function, role function/ physical, role function/emotional, social function, and mental health ($p<0.01$ to $p<0.0004$)
				($p<0.0001$)	Performance status	NR	NR	

N Number of randomized patients, *Hb* hemoglobin, *Hct* hematocrit, *MM* multiple myeloma, *NHL* non-Hodgkin's lymphoma, *HL* Hodgkin's lymphoma, *CLL* chronic lymphocytic leukemia, *DAR* darbepoetin alpha, *CT* chemotherapy, *QOL* quality of life, *NR* not reported, *EPO* epoetin, *LYM* lymphoma, *Lung* lung cancer, *Fe* iron, *ns* not (statistically) significant, *pt(s)* patient(s), *DLBCL* diffuse large B cell lymphoma

[a] Primary outcome

[b] Percent of patients with an increase in hemoglobin of ≥20 g/L

[c] Mean (±standard deviation) change in hemoglobin from baseline

[d] Results reported for the transfusion-independent group

[e] Median change in hemoglobin from baseline

[f] For 38, 44, and 39 evaluable patients in the EPO 10,000 U/kg, EPO titrated dose, and control groups, respectively

[g] Median average increase in hemoglobin per week

[h] Median level of hemoglobin during treatment

[i] Percent of patients with an increase in hemoglobin level of at least 10 g/L after 8 weeks of therapy

[j] Mean change in hematocrit from baseline

difference in the proportion of deaths (65% in the epoetin beta group vs. 63% in the placebo group) or in median survival (17.4 months in the epoetin beta group vs. 18 months in the placebo group, $p=0.76$) [22]. A pooled analysis of four randomized double-blind placebo-controlled trials of individuals with lymphoproliferative disease and solid tumors [21], two of which are included in this systematic review [13, 14], showed no difference in median overall survival for 344 patients with lymphoproliferative malignancies who were randomized either to darbepoetin alpha (30.4 months) or placebo (36.6 months). However, subsequent follow-up of the 344 patients showed that the use of darbepoetin was associated with poorer survival in patients with lymphoproliferative malignancies (hazard ratio 1.37, $p=0.04$) [32, 33]. One randomized controlled double-blind, placebo-controlled trial assessed 989 patients with solid or non-myeloid hematological malignancies who were not receiving chemotherapy or radiotherapy [26]. Survival was inferior for individuals treated with darbepoetin (HR=1.22, 95% CI 1.03–1.45; $p=0.022$), although the authors note that these statistical parameters were less significant when analyses were adjusted for baseline prognostic variables [26]. While the randomized groups were not stratified by specific disease entities, subset analyses suggest that inferior survival differences may be observed for individuals with multiple myeloma, hazard ratio 2.98 (95% confidence interval 1.15 to 7.70) and non-Hodgkin's lymphoma, hazard ratio 2.25 (95% confidence interval 0.67 to 7.55) [26]. Lastly, preliminary results published in abstract form of individuals with diffuse large B cell lymphoma treated with rituxan and CHOP chemotherapy every 14 or 21 days did not demonstrate a difference in survival in patients treated with darbepoetin [31, 33]. Individuals were randomized to receive prophylactic darbepoetin or transfusion and/or darbepoetin or erythropoietin if the hemoglobin concentration was 90 g/L or less or if individuals had symptoms of anemia. Overall survival was 78% in individuals treated with darbepoetin and 70% in the other group (the *p* value was not reported).

Quality of life/performance status

Seven published trials [7, 13, 15, 16, 24–26] and three abstracts [27, 28, 30] reported on quality of life (Table 2). Quality of life was assessed in eight studies [7, 13, 15, 16, 24–27] by the Functional Assessment of Cancer Therapy scales while the methodology could not be determined in the remaining trials [28, 30]. Seven studies were blinded [7, 13, 15, 16, 24, 26, 28]. Quality of life was reported as a primary endpoint in one report [25], a secondary endpoint in seven studies [7, 13, 15, 16, 24, 26, 28], and not stated in two [27, 30]. Six trials reported on patients with multiple

hematological malignancies and/or solid tumors [13, 15, 16, 24–27], whereas three reported on single malignancies, multiple myeloma [7, 30], and chronic lymphocytic leukemia [28]. Seven trials reported an improvement in quality of life [13, 15, 16, 25, 27, 28, 30], whereas three trials reported no improvement in quality of life in patients with multiple myeloma [7, 24] and in patients with hematological and solid tumor malignancies [26]. None of the trials reported on the proportion of patients whose quality of life improved.

Transfusions

Seven randomized controlled trials [6, 7, 13, 15, 16, 24, 31], five of which were double-blind and placebo-controlled [7, 13, 15, 16, 24], reported a statistically significant reduction in the proportion of patients transfused following therapy with erythropoiesis-stimulating agents (Table 2). The reduction in transfusions ranged from 15% to 40%. Two trials [5, 7], which reported on the proportion of patients transfused, solely focused on patients with multiple myeloma and included a total of 216 patients. One of these trials [7] detected a significant decrease in the proportion of patients transfused (28% vs. 47%, p=0.02). A total of 519 patients with multiple myeloma were enrolled in the remaining trials that included patients with other malignancies [6, 13–16, 19]. Four of these trials also detected a difference in the proportion of all patients transfused, favoring erythropoietin/darbepoetin [6, 13, 15, 16]. The use of erythropoietin/darbepoetin has also been shown to significantly decrease the proportion of patients transfused in patients with non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and Hodgkin lymphoma [6, 13, 15, 16, 31]. A total of 445 patients with non-Hodgkin's lymphoma, 227 patients with chronic lymphocytic leukemia, and 46 patients with Hodgkin lymphoma were included in the trials. The absolute risk reduction in transfusions ranged from 15% to 24%, and the number needed to treat to prevent a transfusion ranged from 4 to 6.

The use of erythropoiesis-stimulating agents was not associated with a reduction in the mean/median number of red cells transfused. Three trials assessed the number of units transfused and did not demonstrate a statistically significant difference in units transfused [5, 6, 19].

Change in hemoglobin/hematocrit

All but four studies [6, 17, 18, 30] reported either a statistically significant increase in the hemoglobin concentration or hematocrit or in the proportion of patients with an increase in the hemoglobin concentration or hematocrit with the use of erythropoiesis-stimulating agents (Table 2).

Adverse events

Five placebo-controlled trials provided detailed descriptions of adverse events with erythropoietin [5–7, 16, 18]. Table 3 describes the range of adverse events detailed in those studies. In all trials, there were no statistically significant differences in the frequency of adverse events and mortality between erythropoietin and control groups. Erythropoietin therapy may have contributed to two deaths: an elderly patient who had a stroke [16] and a patient who had a pulmonary embolus [15]. More patients in the erythropoietin arms in the trial by Österborg and colleagues [6] died from infections/septicemia but none were reported to be attributable to the treatment regimens. Two patients had an increase in the level of monoclonal protein coincident with an increase in the erythropoietin dose in the trial by Silvestris and colleagues [18]. One study reported that thromboembolic events occurred more frequently in patients treated with erythropoietin (6%) compared to untreated patients (1%, the p value was not reported) [25].

Four trials reporting adverse events for darbepoetin alpha also did not find a statistically significant difference for mortality or adverse events [13, 14, 26, 31]. Fatigue, fever, nausea, diarrhea, vomiting, dyspnea, and constipation were reported equally in both groups and were the most common adverse events [13, 14]. One trial reported a higher rate of severe, life-threatening or fatal adverse events (40.9% with placebo compared to 47.6% with darbepoetin, the p value was not reported) and serious adverse events (33.8% with placebo compared to 40.8% with darbepoetin, the p value was not reported) in individuals with solid tumors and hematological malignancies treated with darbepoetin [26]. Cardiovascular and thromboembolic events were also higher with darbepoetin, 9.7% compared to 7.7% with placebo (the p value was not reported) [26]. Twenty-two percent of patients died from cancer in the darbepoetin

Table 3 Range of adverse events in published reports with placebo groups

Adverse event	Frequency	
	Erythropoietin (%)	Placebo/control (%)
Fever	7–22	13–17
Disease progression	7–26	3–24
Granulocytopenia	4–20	5–13
Nausea	18	14
Thrombosis	3–7	2–6
Hypertension	4–12	1–2
Infection	1–33	3–16
Skeletal pain	7–10	2–3
Renal insufficiency	12	6
Mortality	2–27	9–28

arm compared to 16% in the placebo arm (the *p* value was not reported) [26]. However, there was no association between cardiovascular and thromboembolic events and a hemoglobin concentration of 130 g/L or higher (hazard ratio 0.43, 95% confidence interval 0.13 to 1.410) [26]. Lastly, one trial published in abstract form demonstrated that cardiac (9% with darbepoetin and 9% for the second group, the *p* value was not reported) and vascular events (8% with darbepoetin and 10% for the second group, the *p* value was not reported) were similar in individuals treated with prophylactic darbepoetin to individuals treated with ESAs or transfusion when their hemoglobin concentration declined. The rate of thromboembolic events was not found to be associated with an increased hemoglobin concentration [31].

Predictors of response

Various parameters have been considered in trying to establish predictors of response to erythropoietin or darbepoetin therapy including an early change in hemoglobin concentration, an increase in reticulocyte count, the platelet count, the pretreatment endogenous erythropoietin level, and the observed/predicted (O/P) erythropoietin ratio (i.e., a ratio that was formulated to determine the appropriate erythropoietin response to anemia) [19]. The utility of any of the above parameters in the prediction of response to erythropoietin or darbepoetin was not prospectively studied in any of the trials.

Discussion

This is the only systematic review that focuses on the role of erythropoiesis-stimulating agents solely in patients with non-myeloid hematological malignancies. Previously published systematic reviews and practice guidelines have evaluated the role of these agents principally in patients both with solid tumors and hematological malignancies [10, 11]. While an argument can be advanced that these data could be generalized to hematologic cancers, it is equally possible that these agents behave differently in patients with blood-related cancers. For this reason, a systematic review specifically addressing this patient population was undertaken.

We found no evidence that the use of erythropoiesis-stimulating agents improved survival in patients with hematologic malignancies. While only one trial published in abstract form included in this systematic review evaluated survival as a primary outcome [31], a total of 1,185 patients were evaluated in four trials, two of erythropoietin and two of darbepoetin, with no evidence of a survival benefit [16, 21, 22, 26]. One trial of erythropoietin suggested that a trend towards a survival benefit was observed in an analysis of cancer patients [16] and another report of darbepoetin did not find a difference in survival [31]. The latter report has not been published and has several methodological limitations including the analysis of the effect of darbepoetin was a secondary and not primary analysis of this study, tumor proliferation [33] and the comparator group also received an erythropoiesis-stimulating agent. Two reports, however, indicated that the use of erythropoiesis-stimulating agents was associated with a poorer survival [26, 32]. In addition, there are reports of at least three randomized trials that have observed either a shortened survival or progression-free survival in patients randomized to receive erythropoietin in trials of breast cancer [34], the anemia associated with lung cancer [35], and head and neck cancer concomitant with radiation therapy [36]. The hemoglobin concentrations achieved with erythropoietin-stimulating agents in all of these trials were higher than 120 g/L. However, the most recent trial with darbepoetin did not show an association between cardiovascular and thromboembolic events and a hemoglobin concentration of 130 g/L or higher (hazard ratio 0.43, 95% confidence interval 0.13 to 1.410) [26]. These results, as well as two additional trials in breast and gynecological cancer, have led the Food and Drug Administration to reaffirm the new labeling that strengthens the boxed warnings that caution should be exerted in prescribing these agents [37]. The Food and Drug Administration strongly recommended that the risks of tumor progression and shortened survival associated with erythropoietin-stimulating agents be discussed with patients [37]. Subsequently, a review of 51 studies to evaluate the risks of venous thromboembolism and mortality rates with erythropoiesis-stimulating agents found an increased mortality and risk of venous thromboembolism with erythropoiesis-stimulating agents [38]. The hazard ratio for mortality with erythropoiesis-stimulating agents was 1.1 (95% confidence interval 1.01–1.20). Although with more judicious use of erythropoiesis-stimulating agents the risks of venous thromboembolism and cancer progression may be lower, these risks should not be minimized with patients.

The impact of erythropoiesis-stimulating agents on quality of life is difficult to assess. Seven trials included in this review reported improvement in some quality of life parameter [13, 15, 16, 25, 27, 28, 30]. However, there are several limitations to the assessment of quality of life in those studies. Those reports did not follow the proposed guidelines for analyzing, interpreting, and reporting quality of life measures [39, 40]. The recommendations for reporting quality of life include reporting of raw scores, reporting of the proportion of patients who improve, detailing methods of handling missing data, and defining clinically important differences. None of the studies included in this systematic review included the proportion

of patients who improved or defined a clinically important difference. One study reported that changes from baseline were significant [25] based on "clinically meaningful levels" [41]. However, these "clinically meaningful levels" have not been correlated with clinical outcomes and thus have not been validated. In addition, details of how missing data were analyzed were only provided by two trials [25, 26]; however, the former trial excluded subscales where more than 50% of data were missing. Missing data can affect the validity of any study, as missing data can reduce the sample size available for analysis, and hence, reduce the power to detect significant differences [42]. This can be particularly problematic for oncology trials because missing values are likely related to the underlying illness, i.e., patients who drop out or miss appointments are likely to be the sicker patients. Given these limitations, we could not come to any definitive conclusions regarding the impact of erythropoiesis-stimulating agents on quality of life in patients with hematologic malignancies. Of note, the American Society of Clinical Oncology and the American Society of Hematology reached a similar conclusion in their evidence-based guidelines on the use of erythropoietin in patients with cancer [11].

We did not address the economic benefit or cost for erythropoiesis-stimulating agents although there are studies addressing the cost effectiveness of these agents. A cost-effectiveness analysis was included in the report of the National Institute for Health and Clinical Excellence's (NICE) appraisal of erythropoietin in patients with cancer [43]. Their estimate was greater than 100,000 pounds sterling (£) per Quality-Adjusted Life Year (QALY). However, estimates of cost effectiveness based on QALY are insufficient because of the limitations in the assessment of quality of life parameters in existing reports. In addition, estimates of cost effectiveness cannot be applicable as erythropoiesis-stimulating agents are potentially associated with reduced survival.

The obvious outcome measure that falls into a category of "other considerations" is the effect of erythropoiesis-stimulating agents on transfusion requirements. This effect is clearer. From the pooled analysis of all eligible trials, erythropoiesis-stimulating agents reduced the proportion of patients requiring transfusion. The absolute risk reduction in transfusions ranged from 15% to 24%, and the number needed to treat to prevent a transfusion ranged from 4 to 6. It should be noted, however, that the difference in the number of units transfused was not statistically significant between groups. The importance of transfusion avoidance as an endpoint can be debated. There are significant limitations to chronic transfusion therapy beyond their cost, notably periodic limited availability, the potential risks of emerging infections, and iron overload. Limitations in availability and utilization of blood products in patients with malignancies can have an impact beyond the cancer system. A strategy of using erythropoiesis-stimulating agents in all anemic patients with cancer in order to avoid or minimize transfusion also has limitations. In the studies identified in this review, rates of transfusion in the placebo or control arms were relatively low (generally less than 50%). Therefore, routine use of these agents would expose a significant proportion of patients to costly and potentially unnecessary treatment.

The tragedy of transfusion-related infection with the human immunodeficiency virus and hepatitis C virus in the 1980s and 1990s led to legislative and judicial considerations of alternatives to transfusion in a number of jurisdictions, including Canada. In Canada, the Commission of Inquiry on the Blood System in Canada recommended that patients be offered alternatives to transfusion [9]. The data we have reviewed support the efficaciousness of using erythropoiesis-stimulating agents as an alternative to transfusion. In the absence of data showing improvements in survival, or of compelling data showing improvements in quality of life, and more data demonstrating an association between mortality and thromboembolic events, the determination of practice policies will need to balance the efficacy related to transfusion reduction and the values placed on this outcome measure.

All but four of the studies included in this review reported increased hemoglobin levels or hematocrit levels with the administration of erythropoiesis-stimulating agents. We did not consider this to be a clinically important endpoint in the absence of associated improvement in a clinically significant endpoint, i.e., survival, quality of life, or transfusion requirement.

This systematic review evaluated trials of erythropoietin as well as darbepoetin. The benefits in hemoglobin level and transfusion reduction were observed with both agents, though the data evaluating erythropoietin were more abundant and mature. Insufficient data exist to allow for a firm recommendation to use one agent over the other.

There are limitations to this systematic review. We did not conduct a meta-analysis on any of the outcomes. The reasons for not performing such an analysis include: (1) the assessment of quality of life had methodological limitations; (2) there was heterogeneity in hemoglobin entry criteria, hemoglobin concentrations for transfusion, the variable use of iron supplementation, and the variable duration of assessment for the outcome of the proportion of patients transfused; and (3) the lack of clinical significance of an increase in the hemoglobin concentration or hematocrit with erythropoiesis-stimulating agents. The Cochrane Collaboration did perform meta-analyses on most outcomes except quality of life as part of their systematic review of

the use of erythropoietin in patients with cancer; however; only a small proportion of patients included had hematologic malignancies [10]. The authors of that review performed subgroup analyses on patients with hematologic malignancies for the outcomes that were included in the meta-analysis. However, because of the limitations previously mentioned, we feel that the most rational and rigorous methodology to analyze the data would not be a meta-analysis. Our results do not differ significantly from that systematic review in that for patients with cancer-related anemia, the use of erythropoietin reduces the proportion of patients who receive transfusions, and the effects of erythropoeisis-stimulating agents on survival need to be further analyzed.

A number of practice guidelines on the use of erythropoietin in patients with cancer have been published by different agencies [11, 43–45], although this is the only systematic review that specifically addresses patients with hematologic malignancies. Those documents differ widely in methodology with some being based on rigorously conducted systematic reviews while others are principally consensus-based. There is general agreement on the interpretation of the data; specifically, the use of erythropoiesis-stimulating agents improves hemoglobin levels and decreases rates of transfusion. Many of those guidelines recommend the use of erythropoiesis-stimulating agents for patients with cancer who are receiving chemotherapy and who have a hemoglobin level less than 100 or 120 g/L. However, one guideline did not recommend the use of these agents [43]. The National Institute for Health and Clinical Excellence's appraisal, based largely on the systematic review of erythropoietin for patients with cancer published by the Cochrane Collaboration, was that erythropoietin should not be recommended for the treatment of anemia induced by cancer treatment except when patients are treated as part of a clinical trial [43]. On the basis of the data analyzed, the NICE panel did not identify an improvement in survival with erythropoiesis-stimulating agents and considered the impact on quality of life to be uncertain. Given the high cost and uncertain benefit, this treatment was not recommended [43].

The differences in recommendations in these documents do not result from fundamental differences in interpretation of the data, but rather on the emphasis that should be placed on endpoints such as transfusion avoidance, as well as considerations such as cost. With emerging evidence that erythropoiesis-stimulating agents may result in disease progression and poorer survival [26, 32], recommendations are likely to be more concordant. The decision of whether to use erythropoiesis-stimulating agents for reduction in the proportion of patients transfused should primarily consider the possibility of poorer survival, the risk of thromboembolic events, the risk of tumor progression, individual patient values, and the likelihood that a patient will require a transfusion as to not expose patients to unnecessary treatment risk and the health care system to additional costs.

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