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Review

Evaluating erythropoietic agents for the treatment of anaemia in the oncology setting

Pere Gascón *

Hospital Clinic, Division of Medical Oncology, IDIBAPS, Institut Clinic Malalties Hemato-Oncològiques (ICMHO), University of Barcelona, 08036 Barcelona, Spain

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Abstract

Anaemia is a common complication of cancer and its treatment. It is also associated with substantial impairment of patient quality of life (QOL). Erythropoietic agents are primary treatment options for cancer-related anaemia (CRA). This review summarises evidence supporting clinical use of the approved erythropoietic agents (epoetin alfa, epoetin beta, darbepoetin alfa). A MEDLINE® search from January 2000 to September 2004 using the search terms "epoetin alfa," "epoetin beta," "darbepoetin alfa," "erythropoietin," and "anaemia" was conducted to identify studies evaluating erythropoietic agents in the treatment of CRA. Recent presentations at professional meetings were also included. Erythropoietic agents increase haemoglobin levels, decrease transfusion requirements, and improve QOL in patients with CRA. However, variations in study design, patient populations, dose titration schedules, and outcome measures among available studies make data comparisons between clinical trials difficult. Head-to-head trials are comparing erythropoietic agents in a randomised setting; other trials are evaluating optimal dosage schedules. Clinically relevant differences among approved erythropoietic agents have not been determined in direct comparative trials; however, epoetin alfa appears to be at least as effective as darbepoetin alfa in treatment of CRA.

Keywords: Darbepoetin alfa; Epoetin alfa; Epoetin beta; Haemoglobin; Quality of life

1. Introduction

Anaemia caused by cancer and its treatment is a common but undertreated complication that adversely affects patients' well-being, quality of life (QOL), and potentially survival [1–3]. Changes in cancer chemotherapy, particularly the introduction of new agents and treatment regimens and the shift towards managing cancer as a chronic disease, have increased the clinical significance of cancer- and chemotherapy-related anaemia (CRA) [4,5]. Because of the infection and immunosuppressive risks associated with blood transfusions, as well as their transient effect on haemoglobin (Hb) levels and amelioration of anaemia, the use of erythropoietic agents has become the new standard of care for patients with CRA. Currently, in Europe, there are three approved erythropoietic agents. Epoetin alfa was the first agent approved in Europe (in 1994) for the treatment of anaemia in adult patients receiving chemotherapy [6], followed more recently by epoetin beta and darbepoetin alfa. Epoetin alfa and epoetin beta are recombinant forms of endogenous erythropoietin, while darbepoetin alfa is a modified erythropoiesis-stimulating protein that contains higher sialic acid carbohydrate content than endogenous erythropoietin, which extends its serum half-life but reduces its binding affinity for the erythropoietin receptor [7–10]. The efficacy of these agents has been demonstrated in clinical trials, but ongoing research is underway to determine optimal dosing regimens that

* Tel./fax: +34 932 275 402.
E-mail address: gascon@clinic.ub.es.

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maximise efficacy while simultaneously optimising flexibility and convenience for patients.

Anaemia definitions vary internationally, with the World Health Organization and the US National Cancer Institute classifying anaemia by grade (0–4, with 0 representing "normal" and 4 the most "severe"). In these classification schemes, more severe anaemia grades are identical in terms of Hb thresholds (6.5–7.9 g/dL for grade 3; <6.5 g/dL for grade 4), but less severe grades are identified by slightly different Hb thresholds. The US National Comprehensive Cancer Network (NCCN) defines anaemia as mild (Hb 10–11 g/dL), moderate (Hb 8–10 g/dL), or severe (Hb < 8 g/dL). The American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) jointly published consensus guidelines on the use of erythropoietic agents in patients with cancer [4]. These guidelines recommend erythropoietic agents as a treatment option for patients with CRA and Hb levels ⩽10 g/dL [4]. For less severe anaemia (Hb >10 and ⩽12 g/dL), the ASCO/ASH guidelines recommend treatment with an erythropoietic agent depending on clinical circumstances [4]. NCCN guidelines provide similar recommendations, although erythropoietic agents are recommended as a treatment option for patients with Hb < 11 g/dL [5]. Both guidelines recommend a target Hb level of 12 g/dL [4,5]. The European Organisation for Research and Treatment of Cancer (EORTC) also recently published guidelines for the use of erythropoietic proteins in anaemic patients with cancer [11]. These guidelines recommend initiating treatment with an erythropoietic protein in patients with cancer and Hb 9–11 g/dL based on anaemia symptoms, regardless of whether the patient is receiving chemotherapy or radiotherapy. The guidelines further state that erythropoietic therapy may be considered in asymptomatic, anaemic patients with Hb 9–11 g/dL to prevent further decreases in Hb, according to individual factors (*e.g.* type/intensity of chemotherapy, baseline Hb). The target Hb recommended by EORTC is 12–13 g/dL, with the major goals of erythropoietic therapy being QOL improvement and prevention of transfusions [11]. As with all the aforementioned guidelines, the EORTC guidelines will need updating on a regular basis, especially with respect to levels of evidence, as newer data become available.

Despite these recommendations and the well-documented benefits of subcutaneous (SC) administration of erythropoietic agents in this setting, CRA continues to be undertreated. This problem is further complicated by confusion regarding the relative efficacy and safety of the approved agents. Trials conducted to date evaluating these agents have often used different outcome measures, inclusion/exclusion criteria, and design features that potentially confound any clinical comparisons between the approved agents. The purpose of this review is to provide a critical analysis of published data regarding the clinical profiles of epoetin alfa, epoetin beta, and darbepoetin alfa for the treatment of CRA. This review includes clinical studies that were identified in a MEDLINE® search using publication dates from January 2000 to September 2004 and the search terms "epoetin alfa," "epoetin beta," "darbepoetin alfa," "erythropoietin," and "anaemia." Only publications relating to the use of these agents in the oncology setting were considered. Recent relevant presentations at professional meetings were also included.

2. Pharmacokinetic/pharmacodynamic properties

Differences in the molecular compositions of epoetin alfa, epoetin beta, and darbepoetin alfa result in pharmacokinetic and pharmacodynamic differences between these agents. Epoetin alfa and epoetin beta demonstrate similar pharmacokinetic profiles in healthy subjects, the primary differences being a greater volume of distribution and prolonged elimination following intravenous administration, and delayed subcutaneous absorption of epoetin beta compared with epoetin alfa [12]. Darbepoetin alfa has two additional N-linked carbohydrate chains, each containing four additional sialic acid residues, compared with recombinant erythropoietin. These modifications result in a two to threefold longer plasma half-life [12–14]. However, the extra carbohydrate chains also give darbepoetin alfa approximately four-fold-lower binding affinity for the erythropoietin receptor than either epoetin alfa or epoetin beta [12,14]. The clinical implications of these pharmacokinetic differences have not yet been definitively established.

3. Clinical efficacy

Since randomised comparative trials of epoetin alfa and darbepoetin alfa have only recently been initiated, balanced assessments regarding the relative therapeutic value of these agents are challenging. Clinical trial design, patient populations, inclusion/exclusion criteria, baseline haematologic status, drug doses and dosage frequency, and dose titration schedules differ widely across these studies. In addition, studies differ with respect to outcome parameters, including definitions of haematologic response, and time at which responses are measured. No direct comparative trials of epoetin beta with another approved erythropoietic agent have been identified.

Table 1 summarises the most frequently evaluated dosage regimens for the three approved erythropoietic agents. The EORTC guidelines recommend that, within reasonable limits of body weight, fixed doses of erythropoietic agents should be used [11]. In Europe, epoetin alfa is approved for the treatment of CRA using a

Table 1
Dosage regimens of erythropoietic agents for the treatment of CRA

Drug	Approved regimens in Europe	Approved regimens in the US	Alternative and investigational dosage regimens
Epoetin alfa	In patients with solid tumours, malignant lymphoma, or multiple myeloma: 150 IU/kg SC TIW, increasing to 300 IU/kg SC TIW[a] [15]	In patients with non-myeloid malignancies: 150 IU/kg SC TIW, increasing to 300 IU/kg SC TIW[a] [17]	60,000 IU QW (induction) followed by 60,000 IU Q2W [18]
	or	*or*	80,000 IU Q3W [19] or 120,000 IU Q3W [20] (maintenance)
	450 IU/kg SC QW[b] [16]	40,000 IU QW, increasing to 60,000 IU QW[a] [17]	
Epoetin beta	In patients with solid tumours: 150 IU/kg IV QW, increasing to 300 IU/kg TIW[a] [21] *or* In patients with lymphoid malignancies: 450 IU/kg QW increasing to 900 IU/kg QW[b] [21] *or* 30,000 IU SC QW[a] [22]	Not approved in US	
Darbepoetin alfa	In patients with non-myeloid malignancies: 2.25 mcg/kg SC QW, increasing to 4.5 mcg/kg QW[a] [23]	In patients with non-myeloid malignancies: 2.25 mcg/kg QW, increasing to 4.5 mcg/kg QW[a] [23]	4.5 mcg/kg or 325 mcg fixed dose QW (induction), then 4.5 mcg/kg or 325 mcg fixed dose Q3W (maintenance) [25]
	or		3 mcg/kg SC Q2W, with titration to 5 mcg/kg Q2W[a] *or*
	Q3W administration[c] [24]		200 mcg Q2W, increasing to 300 mcg Q2W[a] [26]

[a] Dose increased for inadequate haemoglobin response. TIW, three times per week; QW, once weekly; Q2W, every 2 weeks; Q3W, every 3 weeks.
[b] Dosage regimen recently approved by the European Commission. Recommendations for dosage adjustments not publicly available at press time.
[c] Dosage regimen recently approved by the European Commission. Recommendations for precise dose and dosage adjustments not publicly available at press time.

three-times-weekly (TIW) or once-weekly (QW) dosage regimen; darbepoetin alfa for QW or once-every-3 week (Q3W) administration; and epoetin beta for QW administration in patients with lymphoid malignancies. In the US, a QW regimen for epoetin alfa was recently approved, and a Q2W administration schedule for darbepoetin alfa is frequently used in clinical practice [27]. Epoetin beta is not approved for use in the US.

3.1. Treatment of cancer-related anaemia

3.1.1. Epoetin alfa

Randomised, placebo-controlled, and open-label clinical trials of epoetin alfa have enrolled patients with either solid tumours or haematologic (myeloid and non-myeloid) malignancies, and have typically required patients to have a baseline Hb $\leqslant$ 11 g/dL [28–34] (Table 2). In a randomised, controlled, multicentre trial, 375 patients with solid tumours or non-myeloid haematologic malignancies were randomised to receive epoetin alfa 150 IU/kg SC TIW or matching volume of placebo for up to 28 weeks [29]. The epoetin alfa dose was increased to 300 IU/kg SC TIW if Hb had not increased by $\geqslant$1 g/dL at week 4 and reticulocyte count had not increased by $\geqslant$40,000/μL. Compared with placebo, patients receiving epoetin alfa had significantly greater increases in Hb (2.2 g/dL *versus* 0.5 g/dL; $P < 0.001$), fewer transfusions (24.7% *versus* 39.5%; $P = 0.0057$), and were more likely to achieve a $\geqslant$2-g/dL increase in Hb (70.5% *versus* 19.1%; $P < 0.001$) [29]. In addition, epoetin alfa was associated with significant (range, $P = 0.0007$ to $P = 0.0048$) improvements in all primary QOL endpoints compared with placebo [29]. Notably, there was a strong and statistically significant (range, $P = 0.0002$ to $P = 0.0325$) correlation between Hb changes and changes in QOL parameters [29].

Epoetin alfa appears to produce similar benefits in patients with CRA irrespective of whether they are receiving chemotherapy [30]. In a prospective, multicentre, open-label trial, treatment with epoetin alfa 150 IU/kg SC TIW for 16 weeks resulted in a mean Hb increase of 2.5 g/dL from baseline to study end in 182 cancer patients who did not receive chemotherapy, compared with a mean Hb increase of 2.8 g/dL in 218 patients who did receive chemotherapy [30].

Once-weekly dosage regimens for epoetin alfa have also been studied, which offer more convenience for patients and clinicians, and epoetin alfa 40,000 IU SC QW

Table 2
Phase III/IV studies of epoetin alfa (EPO-alfa) for chemotherapy-related anaemia

Reference	Study design	*N*[a]	Dose	Mean Hb change BL → final (g/dL)	Response rate	RBC transfusions	Mean QOL improvement BL → final
Non-myeloid malignancies							
Littlewood [29]	Randomised, multicentre, double-blind, placebo-controlled	EPO-alfa: 251	150–300 IU/kg SC	EPO-alfa: 2.2	EPO-alfa: 71%[b]	Post Day 28 transfusion rate: 25% *versus* 40% for placebo	EPO-alfa: LASA↑ 4.8–8.1 mm; FACT-An ↑ 2.5–4.0 points
		Placebo: 124	TIW × 28 weeks	Placebo: 0.5	Placebo: 19%[b]		Placebo: LASA↓ 5.8–6.0 mm; FACT-An↓ 2.2–3.6 points
Gabrilove [33]	Community-based, multicentre, open-label, non-randomised	2964	40,000–60,000 IU SC QW × 16 weeks	1.8	68%[c]	9% ↓ from BL → Month 4	LASA ↑ 19–30%; FACT-An ↑ 6.0 points
Quirt [30]	Multicentre, open-label, non-randomised	Non-CT cohort: 182	150–300 IU/kg SC	Non-CT cohort: 2.5	Non-CT cohort: 48%[b]	Non-CT cohort: 21% ↓ from BL → Month 4	Non-CT cohort: LASA ↑ 12–14 mm; FACT-An ↑ 3–8 points
		CT cohort: 218	TIW × 16 weeks	CT cohort: 2.8	CT cohort: 63%[b]	CT cohort: 25% ↓ from BL → Month 4	CT cohort: LASA ↑ 13–14 mm: FACT-An ↑ 4–11 points
Shasha [34]	Community-based, multicentre, open-label, non-randomised	442	40,000–60,000 IU SC QW × 16 weeks	1.9	74%[c]	5% ↓ from BL → Month 4	LASA ↑ 14.2–16.5 mm
Haematologic malignancies							
Littlewood [37]	Subset analysis of a randomised, multicentre, double-blind, placebo-controlled study	EPO-alfa: 115	150–300 IU/kg	EPO-alfa: 2.2	EPO-alfa: 75%[b]	Post Day 28 transfusion rate: 25% *versus* 43% for placebo	EPO-alfa: LASA ↑ 9.0–11.6 mm; FACT-An Fatigue ↑ 4.3 points; FACT-G ↑ 5.8 points
		Placebo: 58	SC TIW × 28 weeks	Placebo: 0.3	[73%[d]] Placebo: 17%[b][15%[d]]		Placebo: LASA ↓ 2.5–5.2 mm; FACT-An Fatigue ↓ 0.2 points; FACT-G ↑ 1.1 points
Dammacco [28]	Randomised, multicentre, placebo-controlled	EPO-alfa: 69	150–300 IU/kg SC	EPO-alfa: 1.8	EPO-alfa: 58%[b][46%[d]]	Transfusion rate during Months 2 and 3: 28% *versus* 47% for placebo	Specific values not reported
		Placebo: 76	TIW × 12 weeks	Placebo: 0.0	Placebo: 9%[b][3%[d]]		

Non-small-cell lung cancer							
Crawford [31]	Subset analysis of 3 community-based, multicentre, open-label, non-randomised studies	1748	150–300 IU/kg SC TIW *or* 10,000–20,000 IU SC TIW *or* 40,000–60,000 IU SC QW × 16 weeks	1.9	Not reported	12% ↓ from BL → Month 4	LASA ↑ 9.2–11.8 mm
Breast cancer							
Demetri [32]	Subset analysis of 3 community-based, multicentre, open-label, nonrandomised studies	1280	150–300 IU/kg SC TIW *or* 10,000–20,000 IU SC TIW *or* 40,000–60,000 IU SC QW × 16 weeks	1.9	51%[b][68%[c]]	10% ↓ from BL → Month 4	LASA ↑ 11.6–14.4 mm

Hb, haemoglobin; BL, baseline; RBC, red blood cell; QOL, quality of life; SC, subcutaneously; TIW, three times weekly; LASA, Linear Analog Scale Assessment; FACT, Functional Assessment of Cancer Therapy; An, anaemia; QW, once weekly; G, general.

[a] Number of patients evaluable for efficacy.

[b] Hb increase ⩾2 g/dL from baseline during the study.

[c] Hb increase ⩾2 g/dL from baseline or Hb ⩾ 12 g/dL during the study.

[d] Hb ⩾ 12 g/dL during the study.

has recently been approved in the US for patients with CRA. Two large, open-label, community-based studies have evaluated the efficacy of epoetin alfa. The 40,000 IU SC QW dose was escalated to 60,000 IU SC QW for Hb increases ⩽1 g/dL after 4 weeks of treatment in more than 3300 cancer patients with baseline Hb levels ⩽11 g/dL who were receiving chemotherapy alone [33] or in combination with radiation [34]. Similar to the results from studies evaluating TIW schedules, mean increases in Hb were 1.8 and 1.9 g/dL, respectively [33,34]. Significant increases in Hb from baseline were evident within 2–4 weeks of treatment initiation [33,34], with a mean Hb increase of 1.1 g/dL reported at 4 weeks [35]. The number of epoetin alfa patients requiring transfusions and the number of units transfused decreased by more than half compared with baseline after 4 months of therapy [33,34]. Another study also showed that a QW epoetin alfa regimen increased Hb levels by 3.1 g/dL after 12 weeks, and improved overall QOL in 100 cancer patients with CRA who were not receiving chemotherapy or radiation [35].

In a recently published, randomised, double-blind, placebo-controlled, multicentre trial, 344 patients with advanced cancer and anaemia (Hb < 11.5 g/dL for men and <10.5 g/dL for women) undergoing chemotherapy received either epoetin alfa 40,000 IU SC QW or placebo for up to 16 weeks [36]. Epoetin alfa recipients also received supplemental iron. After the first month, the epoetin alfa dose was increased to 60,000 IU SC QW if Hb had not increased by >1 g/dL or if the patient required a blood transfusion. Patients in the epoetin alfa group had a mean increase in Hb of 2.8 g/dL, significantly greater than the 0.9 g/dL for the placebo group ($P < 0.0001$). In addition, significantly fewer epoetin alfa patients required transfusions (39.6% *versus* 25.3%; $P < 0.005$). However, unlike the earlier study of the TIW regimen, there was no difference between groups in QOL endpoints. This may have been attributable in part to the fact that transfusions were allowed in both groups at physician discretion [36].

3.1.2. Epoetin beta

Several randomised trials have shown epoetin beta to be effective in treating CRA in patients with solid tumours or haematologic malignancies [8,38–44] (Table 3). In a recent summary of trials including patients with solid tumours, epoetin beta (100–200 IU/kg SC TIW) elicited mean Hb increases of 0.89–2.7 g/dL from baseline to last assessment, with study durations ranging from 8 to 24 weeks [8]. Epoetin beta was also associated with decreases in transfusion requirements of 37–90% compared with no treatment [8].

In a randomised, double-blind, placebo-controlled trial that enrolled 349 patients with transfusion-dependent haematologic malignancies, epoetin beta 150 IU/kg SC TIW improved haematologic parameters and

Table 3
Phase III/IV studies of epoetin beta (EPO-beta) for chemotherapy-related anaemia

Reference	Study design	Tumour type	Treatment	Mean Hb change BL → final (g/dL)	Response rate	RBC transfusions	Mean QOL improvement BL → final
Solid tumours							
Johansson [42]	Randomised	Metastatic, hormone-refractory prostate cancer	EPO-beta 1000 IU TIW ($n = 90$) or 5000–10,000 IU TIW ($n = 90$) × 12 weeks	Not reported	1 K: 25%[b] 5 K: 43%[b]	1 K: 54% 5 K: 40%	EORTC QLQ-C30 improvements: 1 K: 0.7–8.4 points 5 K: 2.7–7.9 points
Kunikane [43]	Randomised, double-blind, placebo-controlled	Non-small-cell lung cancer	EPO-beta 200 IU/kg TIW ($n = 18$) or EPO-beta 100 IU/kg TIW ($n = 16$) or placebo ($n = 19$) × 8 weeks	EPO-beta 200: 1.7 EPO-beta 100: 0.9 Placebo: −0.7	Not reported	EPO-beta 200: 6% EPO-beta 100: 13% Placebo: 0%	Not an endpoint
Olsson [44]	Randomised	Metastatic breast cancer	EPO-beta 1000 IU TIW ($n = 90$) or 5000–10,000 IU TIW ($n = 90$) × 24 weeks	1 K: 1.7 5 K: 2.3	1 K: 51%[b] [68%[c]] 5 K: 58%[b] [66%[c]]	1 K: 36% 5 K: 34%	EORTC QLQ-C30 Global QOL improvements: 1 K: 53%[a] 5 K: 35%[a]
Haematologic malignancies							
Cazzola [39]	Randomised, open-label, multicentre	NHL, MM, CLL	EPO-beta 30,000 IU QW–30,000 IU twice weekly ($n = 115$) or 10,000–20,000 IU TIW ($n = 114$) × 16 weeks	Not reported	30 K: 72%[d] 10 K: 75%[d]	30 K: 9% 10 K: 14%	Not an endpoint
Glossmann [41]	Randomised, controlled	Hodgkin's disease, NHL	EPO-beta 10,000 IU TIW ($n = 20$) or control ($n = 24$) until end of sequential high-dose chemotherapy regimen	EPO-beta: −2.3 Control: −2.7	Not reported	EPO-beta: 75% Control: 92%	EORTC QLQ-C30 changes: EPO-beta: −18.9 to +1.6 points Control-b: −39.4 to −6.9 points
Österborg [38]	Randomised, double-blind, multicentre, placebo-controlled	NHL, MM, CLL	EPO-beta 150–300 IU/kg TIW ($n = 170$) or placebo ($n = 173$) × 16 weeks	Not reported	EPO-beta: 67%[d] Placebo: 27%[d]	EPO-beta: 33% Placebo: 52%	EPO-beta: FACT An ↑14.8 points; FACT-G ↑ 6.5 points; FACT-Fatigue ↑ 5.2 points Placebo: FACT-An ↑ 8.7 points FACT-G ↑ 3.1 points; FACT-Fatigue ↑ 3.0 points
Solid tumours or haematologic malignancies							
Boogaert [40]	Randomised, open-label, multicentre, controlled	NHL, MM, CLL, or any solid tumour	EPO-beta 150–300 IU/kg TIW ($n = 133$) or control ($n = 129$) × 12 weeks	EPO-beta: 2.1 Control: 0.9	EPO-beta: 47% Control: 13%	EPO-beta: 22% Control: 43%	EPO-beta: SF-36 ↑ 3.0 points[a]; FACT-An ↑ 0.8 points[a]; FACT-Fatigue ↑ 6.0 points[a]; LASA ↑ 12 mm[a] Control: SF-36 ↓ 1.5 points[a]; FACT-An ↓ 0.2 points[a]; FACT-Fatigue ↑ 0.5 points[a]; LASA ↓ 0.5 mm[a]

Hb, haemoglobin; BL, baseline; RBC, red blood cell; QOL, quality of life; TIW, three times weekly; EORTC, European Organization for Research and Treatment of Cancer; NHL, non-Hodgkin's lymphoma; MM, multiple myeloma; CLL, chronic lymphocytic leukaemia; FACT, Functional Assessment of Cancer Therapy; An, anaemia; G, general; SF-36, Short Form 36; LASA, Linear Analog Scale Assessment.

[a] Estimated from a graph.

[b] Increase in Hb $\geqslant$ 2 g/dL from baseline.

[c] Increase in Hb $\geqslant$ 1 g/dL from baseline.

[d] Increase in Hb $\geqslant$ 2 g/dL from baseline without need for transfusion.

QOL [38]. Patients treated with epoetin beta had a significantly higher transfusion-free survival rate (66.7%) compared with controls (47.6%; $P = 0.0012$) [38]. Epoetin beta was also associated with a significantly higher response rate (no transfusion requirement and a $\geqslant$2-g/dL increase in Hb) compared with placebo (67% *versus* 27%; $P < 0.0001$) [38]. Significant improvements in QOL (measured by the Functional Assessment of Cancer Therapy-Anemia [FACT-An] and FACT-General [FACT-G] scales) in favour of epoetin beta were evident by week 12 of treatment [38].

A QW epoetin beta dosage regimen was recently compared with the TIW regimen in an effort to establish comparable efficacy between these schedules in patients with CRA. In an open-label trial, 241 patients with lymphoproliferative malignancies with baseline Hb 9–11 g/dL and low-serum erythropoietin levels (<100 mU/mL) were randomised to epoetin beta 10,000 IU SC TIW or 30,000 IU SC QW [39]. The investigators reported no significant differences between groups regarding changes in Hb levels, response rates, or blood transfusion requirements [39]. The median time to Hb increase of $\geqslant$1 g/dL was 4.1 weeks for both the TIW and QW regimens [45]. The authors concluded that epoetin beta administered QW is an effective and convenient treatment for anaemia in patients with lymphoproliferative malignancies and defective endogenous erythropoietin production [39]. However, a recent critical review of this study highlighted several deficiencies in study design and analysis that bring these conclusions into question [46]. These limitations include lack of sufficient statistical power to detect significant differences between groups, a QW group that was not entirely QW (since some patients in this group who did not demonstrate an adequate haematologic response were switched to twice-weekly dosing), and a carefully selected patient population with restrictive exclusion criteria that predicted a higher probability of response. Patients were excluded if they had Hb <9 g/dL, transfusion history within 2 months of baseline, or serum erythropoietin level >100 mU/mL [46]. Nevertheless, the 30,000 IU SC QW regimen of epoetin beta has recently received European marketing approval for anaemic patients with lymphoid malignancies [22].

3.1.3. Darbepoetin alfa

In several dose-ranging studies, darbepoetin alfa was shown to improve haematologic parameters in a dose-dependent manner in patients with solid tumours and non-myeloid haematologic malignancies [47–49]. In one study, darbepoetin alfa 0.5–4.5 mcg/kg SC administered QW elicited mean Hb increases from baseline ranging from 1.45 to 2.91 g/dL after 12 weeks in patients with non-myeloid malignancies [49]. Importantly, the largest Hb increase was only observed at the highest dose level (4.5 mcg/kg SC QW), which is double the US-approved dose for darbepoetin alfa. At the approved darbepoetin alfa dose (2.25 mcg/kg SC QW) patients demonstrated a mean Hb increase from baseline of 2.07 g/dL. Further, the mean change from baseline was calculated using the last available Hb value in the absence of a transfusion in the preceding 28 days. The median time to haematopoietic response (a $\geqslant$ 2-g/dL increase in Hb level or an Hb level $\geqslant$12 g/dL in the absence of a transfusion in the preceding 28 days) was also dose-dependent and ranged from 50 days (~7 weeks) in the lowest dose group to 27 days (~4 weeks) in the highest dose group. Patients receiving the US-approved dose had a median time to response of 36 days (~5 weeks) [49].

The efficacy of QW darbepoetin alfa has been demonstrated in two randomised, double-blind placebo-controlled phase III trials in patients with lung cancer ($n = 320$) [50] and lymphoproliferative malignancies ($n = 344$) [51] (Table 4). In both trials, patients were required to have cancer- or chemotherapy-related anaemia (Hb $\leqslant$ 11 g/dL) and expected to receive $\geqslant$12 additional weeks of chemotherapy [50,51]. Patients were randomised 1:1 to receive darbepoetin alfa 2.25 μg/kg SC QW or placebo for 12 weeks [50,51]. In the first trial, patients in the darbepoetin alfa group had significantly fewer transfusions (27% *versus* 52%; $P < 0.001$), fewer units of red blood cells transfused (0.67 *versus* 1.92; $P < 0.001$), and a higher rate of haematopoietic response (66% *versus* 24%; $P < 0.001$) compared with placebo patients [50]. Similar results were reported in the second trial; 60% of patients receiving darbepoetin alfa had a haematopoietic response, compared with 18% of placebo patients ($P < 0.001$) [51]. The mean increase in Hb level from baseline to last value was 1.8 g/dL in the darbepoetin alfa group and 0.2 g/dL in the placebo group [51]. However, darbepoetin alfa treatment was not associated with significant improvements in QOL endpoints (FACT-Fatigue subscale scores) compared with placebo in either study [50,51]. Hedenus and colleagues [51] demonstrated a statistical difference in FACT-Fatigue scores with darbepoetin alfa *versus* placebo after adjusting for differences in baseline scores, although this analysis was not part of the planned statistical analysis. These investigators also showed a statistically significant ($P < 0.001$) correlation between changes in Hb levels and FACT-Fatigue scores over the treatment period.

3.1.4. Alternative dosage regimens

Alternative dosage regimens for the approved erythropoietic agents are under investigation. In particular, preliminary studies are assessing whether higher initial doses of these agents, followed by less frequent maintenance dosing (sometimes termed "front-loading") can shorten the time to haematologic response, increase overall response rate, improve convenience, and allow

Table 4
Phase III studies of darbepoetin alfa (DARB) for chemotherapy-related anaemia

Reference	Study design	N[a]	Dose	Mean Hb change BL → final (g/dL)	Response rate	RBC transfusions	Mean QOL improvement BL → final
Lympho proliferative malignancies							
Hedenus [51]	Multicentre, randomised, double-blind, placebo-controlled	DARB: 174 Placebo: 170	2.25–4.5 mcg/kg SC QW × 12 weeks	DARB: 1.8 Placebo: 0.2	DARB: 60%[b] [65%[c]] Placebo: 18%[b] [24%[c]]	Transfusion rate Week 5 to end of treatment: 31% *versus* 48% for placebo	Overall mean ↑ in FACT-Fatigue (primary QOL assessment) not provided
Lung cancer							
Vansteenkiste [50]	Multicentre, randomised, double-blind, placebo-controlled	DARB: 156 Placebo: 158	2.25–4.5 mcg/kg SC QW × 12 weeks	Not reported	DARB: 66%[c] Placebo: 24%[c]	Transfusion rate Week 5 to end of treatment: 27% *versus* 52% for placebo	FACT-Fatigue ↑ in 56% of patients *versus* 44% of placebo patients, with a ⩾25% ↑ in 32% *versus* 19% of patients

Hb, haemoglobin; BL, baseline; CT, chemotherapy; RBC, red blood cell; QOL, quality of life; SC, subcutaneously; Q2W, once every 2 weeks; FACT, Functional Assessment of Cancer Therapy; QW, once weekly.
[a] Number of patients evaluable for efficacy.
[b] Hb increase ⩾2 g/dL from baseline during the study independent of transfusion within 28 days.
[c] Hb increase ⩾2 g/dL from baseline or Hb ⩾12 g/dL during the study independent of transfusion within 28 days.

greater dosage flexibility. For example, some studies are evaluating the efficacy of epoetin alfa 60,000 IU SC QW to attain a target Hb of 12 g/dL within 12 weeks followed by maintenance doses of 60,000 IU SC to 120,000 IU SC Q2W or Q3W [18–20].

Similarly, front-loaded schedules of darbepoetin alfa have also been designed to produce accelerated anaemia correction, followed by lower doses to maintain adequate Hb levels for effective erythropoiesis. Such regimens have incorporated either a weight-based dose (4.5 μg/kg SC) or a fixed dose (325 μg SC) administered QW until Hb levels reach 12 g/dL, followed by a lower or less frequent maintenance dose [25,52]. These regimens appear to be effective in producing an Hb response in more than half of patients during the correction phase [25,52]. The Hb levels attained during the correction phase have generally been maintained during the maintenance phase [25,52]. In addition, a Q3W administration schedule of darbepoetin alfa was recently approved in Europe [24]. However, further studies are needed to determine the efficacy and safety of front-loaded dosage regimens of erythropoietic agents [11].

3.1.5. Effects on survival

Anaemia may be an independent prognostic factor for survival in patients with cancer. A quantitative review of the literature indicated an overall estimated hazard rate ratio of death, after adjusting for various factors as reported in each study evaluated, of 1.65 for patients with anaemia and cancer (including lung cancer, head and neck cancer, prostate cancer, and lymphoma) *versus* those without anaemia [3]. In a randomised, placebo-controlled trial of epoetin alfa TIW, Kaplan–Meier estimates showed a trend in overall survival favouring epoetin alfa ($P = 0.13$), with Cox regression analysis demonstrating an estimated hazard ratio of 1.309 ($P = 0.052$) [29]. Although this study was not prospectively powered to assess survival and the protocol did not control for factors that may influence survival (*e.g.*, disease stage, bone marrow involvement), these findings suggested that the mortality risk during the median 26-month follow-up period could have been up to 31% greater for patients receiving placebo than for those receiving epoetin alfa [29].

Subsequently, several studies were initiated to evaluate the efficacy of earlier initiation of erythropoietic agents to maintain Hb, reduce transfusions, and maintain or improve QOL in patients with cancer who were not yet anaemic. Treatment with epoetin alfa was initiated either in patients with Hb levels >10.5 g/dL [53–55] or at the start of chemotherapy in patients with Hb levels ⩾12 and <15 g/dL [56–58]. Data from a randomised, placebo-controlled trial demonstrated that early intervention with epoetin alfa resulted in higher Hb levels and response rates and lower transfusion rates compared with later intervention (*i.e.*, when Hb levels decreased to ⩽10.5 g/dL), while maintaining QOL [55]. Results of prospective studies support these findings and suggest that early treatment with epoetin alfa results in significant increases in Hb, reduced transfusion rates, and improvements in QOL compared with waiting until anaemia becomes more severe (*i.e.*, <9–10 g/dL) [53–58].

While these results are intriguing, none of these studies were powered to evaluate the impact of epoetin alfa on survival. A meta-analysis of 8 randomised clinical trials enrolling 1624 patients with CRA showed that epoetin alfa was associated with a strong trend toward improved survival compared with the control group (hazard ratio = 0.80), although the difference did not quite achieve statistical significance (95% CI for hazard ratio = 0.65, 1.00) [59].

In contrast to these positive results, the publication of two studies beyond the correction of anaemia showing increased mortality in patients receiving early treatment with erythropoietic agents has raised concerns about the safety of this investigational approach [60,61]. In a multicentre, double-blind, randomised, placebo-controlled trial, 351 patients (Hb < 12 g/dL [women] or <13 g/dL [men]) with carcinoma of the head and neck received radiotherapy concomitantly with subcutaneous epoetin beta 300 IU/kg SC TIW ($n = 180$) or matching placebo ($n = 171$) [60]. In this study, 82% of epoetin beta recipients achieved Hb levels >14 g/dL (women) or >15 g/dL (men), compared with 15% of placebo recipients. However, loco-regional progression-free survival was lower for epoetin beta than for placebo (adjusted relative risk, 1.62; $P = 0.0008$) and, when measured separately, relative risks for loco-regional progression and survival were 1.69 ($P = 0.007$) and 1.39 ($P = 0.02$), respectively. The study design allowed patients with near-normal Hb levels to be treated to high target Hb levels (mean Hb at week 9, 15.4 g/dL), in addition to allowing Hb increases ⩾2 g/dL during a 1-week period. The relative contribution of these rapid Hb increases to the mortality outcome in this study is unclear, particularly since the number of patients achieving a rapid Hb increase was not reported. Differences in mortality also may have resulted in part from differences in baseline characteristics between the treatment groups.

Another recent, double-blind, randomised, placebo-controlled study in 939 patients with metastatic breast cancer receiving epoetin alfa 40,000 IU SC QW initiated at the start of chemotherapy and continued for up to 12 months was terminated early because of a significantly higher mortality rate observed in the epoetin alfa group compared with placebo ($P = 0.0117$) [61]. There were no upper or lower limits for baseline Hb level in this study, although the mean baseline Hb level was 12.5 g/dL for each group, and the goal of epoetin alfa therapy was to maintain Hb levels ⩾12 and ⩽14 g/dL [62]. Unfortunately, analysis of survival data was limited by the study design, which did not incorporate prospective collection of many important prognostic variables that may have affected the study outcome [61]. Further, between-group mortality differences were reported primarily within the first 4 months of treatment, with most deaths attributed to disease progression [61]. Reasons for the observed differences in mortality remain uncertain, but it appears likely that increased thrombovascular events associated with this investigative use of erythropoietic treatment beyond correction of anaemia may have played a role. Treatment differed from the approved use of erythropoietic therapy for chemotherapy-associated anaemia in that target Hb levels were relatively high and treatment continued for a year, regardless of chemotherapy. It appears that treating patients to Hb levels of 12–13 g/dL is clinically appropriate to optimise QOL outcomes; however, treating to higher Hb levels beyond anaemia correction cannot be recommended at this time. The use of erythropoietic agents to improve survival or response to cancer treatment in anaemic patients with cancer is also currently not recommended [11].

4. Comparative trials

Challenges in comparing data from studies of erythropoietic agents are due in part to the fact that these studies often did not use consistent methodology to analyze patient populations and define eligibility criteria (including definition of anaemia and baseline Hb level), definitions and time points of haematologic response, and extent of follow-up (trial duration). Also, efficacy analyses varied because of disparities in protocol-defined evaluable patient populations. These discrepancies have created significant challenges in understanding, interpreting, and applying the results of these studies to clinical practice. In an effort to overcome these challenges, several retrospective studies of data from clinical trials have compared the therapeutic value of epoetin alfa and darbepoetin alfa in patients with CRA. In general, these studies have shown similar efficacy for QW epoetin alfa and Q2W darbepoetin alfa [27,63–65], although interpretation of these findings is limited by a variety of factors. In particular, the analysis by Schwartzberg and co-workers [27] did not disclose the mean duration of epoetin alfa or darbepoetin alfa therapy, or the mean duration and number of chemotherapy cycles for each treatment group. Further, there was an imbalance between treatment groups in terms of chemotherapy frequency (more epoetin alfa patients received chemotherapy QW, whereas more darbepoetin alfa patients received chemotherapy Q4W) and epoetin alfa patients who received treatment through week 12 and response information throughout the treatment period had a higher mean baseline Hb than the corresponding darbepoetin alfa population (10.4 *versus* 9.8 g/dL).

Data from two completed head-to-head studies of epoetin alfa and darbepoetin alfa has also been recently reported. One is a single, randomised, open-label, multicentre, phase III study (supported by Ortho Biotech Clinical Affairs, LLC, Bridgewater, NJ, USA) [66], and the other is a pooled analysis of data from three identically designed, randomised, open-label, multicentre,

phase II studies (supported by Amgen Inc., Thousand Oaks, CA, USA) [67]. In both studies, patients were randomised 1:1 to receive epoetin alfa 40,000 IU SC QW or darbepoetin alfa 200 mcg SC Q2W for up to 16 weeks. In the pooled analysis, dose escalation was permitted after 4 weeks for both agents if Hb increase was <1 g/dL [67]. In the single phase III study, dose escalation was permitted after 4 weeks of epoetin alfa (to 60,000 IU SC QW) and after 6 weeks of darbepoetin alfa (to 300 mcg SC Q2W), in line with US ASCO/ASH clinical practice guidelines [66]. The doses chosen for evaluation in both studies were based on the most common doses used in clinical oncology practice in the US. In the pooled analysis, efficacy data were reported for 157 patients receiving darbepoetin alfa and 155 patients receiving epoetin alfa (Table 5) [67]. Mean baseline Hb was 10.4 g/dL in both groups, and mean Hb increase (independent of transfusions within 28 days) from baseline to the end of treatment was 1.5 g/dL with epoetin alfa and 1.4 g/dL with darbepoetin alfa. The percentage of patients requiring a transfusion from baseline to the end of treatment was 16% for darbepoetin alfa and 17% for epoetin alfa [67]. At preliminary analysis of the phase III study, 147 patients receiving epoetin alfa and 142 receiving darbepoetin alfa had a mean baseline Hb of 10.2 and 10.1 g/dL, respectively [66]. From Day 29 to study end, 9.5% of epoetin alfa patients ($n = 148$) and 16.8% of darbepoetin alfa patients ($n = 143$) received transfusions. Mean Hb increase (independent of transfusions within 28 days) after 4 weeks of treatment was 0.9 g/dL with epoetin alfa ($n = 131$) and 0.4 g/dL with darbepoetin alfa ($n = 128$). After 8 weeks of treatment, mean Hb increase was 1.4 g/dL ($n = 95$) for epoetin alfa and 0.8 g/dL ($n = 87$) for darbepoetin alfa [64]. The incidence of thrombovascular events (TVEs) was low in both studies, and was similar between the two treatment groups.

Table 5
Clinical results from direct comparative trials

	Waltzman [66] (*n*)	Schwartzberg [67] (*n*)
Baseline Hb, mean ± SD, g/dL		
Epoetin alfa	10.2 ± 0.8 (147)	10.4 ± 0.8 (155)
Darbepoetin alfa	10.1 ± 0.8 (142)	10.4 ± 0.8 (157)
Mean Hb increase from baseline to last assessment, g/dL		
Epoetin alfa	1.4 (38)	1.5 (155)
Darbepoetin alfa	1.1 (26)	1.4 (157)
Haematologic response rate, % of patients[a]		
Epoetin alfa	50.5 (133)[c]	NA
Darbepoetin alfa	38.0 (129)[c]	NA
Haematopoietic response rate, % of patients[b]		
Epoetin alfa	NA	72 (155)
Darbepoetin alfa	NA	69 (157)
Patients receiving transfusion, %		
Epoetin alfa	9.5[d] (148)	17 (155)
Darbepoetin alfa	16.8[d] (143)	16 (157)

Hb, haemoglobin; SD, standard deviation, NA = not available.
[a] Hb increase ⩾1 g/dL from baseline.
[b] Hb ⩾ 12 g/dL or Hb increase ⩾2 g/dL from baseline.
[c] Modified intent-to-treat population (all randomised patients with ⩾1 dose of study drug and ⩾1 postbaseline Hb value or transfusion).
[d] From Day 29 to study end.

5. Conclusions

Erythropoietic agents have a well-established efficacy for the treatment of cancer- and chemotherapy-related anaemia, eliciting improvements in haematologic parameters and decreasing transfusion requirements. Of the three approved erythropoietic agents, only epoetin alfa and epoetin beta have been associated with statistically significant improvements in *a priori* QOL endpoints compared with placebo in randomised-controlled clinical trials. Although the optimal dosage regimens for all three agents remain to be determined, less frequent dosing schedules for both epoetin alfa and darbepoetin alfa appear to be as effective as the approved regimens. Challenges in comparing these agents include differences in clinical trial design, patient populations, dose titration schedules, and clinical endpoints. Another issue to be resolved is the clinical significance of an earlier Hb increase *versus* the Hb increase achieved overall. It has recently been suggested that an earlier Hb response leads to better clinical outcomes [68]. Publication of the full results of the direct comparative trial supported by Ortho Biotech is eagerly anticipated in the continuing efforts to determine whether there are clinically relevant differences between erythropoietic agents.

Conflict of interest statement

Dr. Gascón has received honoraria from Amgen Inc., Janssen-Cilag Ltd., Johnson and Johnson Pharmaceuticals LLC, and Roche Laboratories Inc. This study was supported by Johnson & Johnson Pharmaceutical Services, LLC.

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