Erythropoietic Therapy for Cancer-related Anemia

a report by

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Introduction

Anemia is the most common hematologic abnormality seen in malignant conditions, occurring in more than 50% of patients.[1] This carries a prevalence in the US approaching 900,000[2] and leads to debilitating symptoms, impaired health-related quality of life (HRQOL), and possible causative roles in reduced survival outcomes and cognitive impairment with chemotherapy. Approximately three-quarters of anemic cancer patients are considered as having chemotherapy-induced anemia (CIA) with the remainder designated as the chronic anemia of cancer (AoC).[3]

In the setting of cancer, anemia is prevalent due to many possible etiologic factors including blood loss, nutritional deficiency, hemolysis, hypersplenism, hemophagocytosis, and impairment of bone marrow function through such mechanisms as myelosuppression, tumor involvement, hypoplasia, myelofibrosis, and myelodysplasia. However, even in the absence of these complicating factors, anemia remains prevalent and, as such, comprises one subset of the anemia of chronic disease.[4] Inflammatory cytokines, especially interleukin (IL-1), interferon-gamma (IFN-γ), and tumour necrosis factor (TNF), reduce erythropoietin (EPO) production, suppress the bone marrow's response to EPO, and alter ferrokinetics.[5] The majority of anemic cancer patients will not represent a 'pure' anemia of cancer as approximately 75% will have had chemotherapy and/or irradiation at some point historically,[6] with the associated myelosuppresssion from these modalities.

Erythropoietin

While it had been recognized for almost a century that a circulating substance regulated mammalian erythropoiesis, the glycoprotein EPO was not isolated until Miyake[7] did so in 1977 from the urine of subjects with aplastic anemia, owing to EPO's normal presence in such minute quantities. By 1985, EPO DNA probes were employed to isolate and then clone the gene.[8,9] Then, with incredible rapidity, recombinant human (rh)EPO was produced by recombinant DNA technology, employed in clinical trials, and gained regulatory approval in 1989 as epoetin alfa for the treatment of anemia in dialysis-dependent end-stage renal disease.

EPO is a 30.4kDA heavily glycosylated protein hormone[7] and is the primary regulator of erythropoiesis in mammalian systems. Structurally, the molecule has an invariant 165 amino acid single polypeptide chain, comprising 60% by weight, with the remainder of the molecule composed of carbohydrate. The carbohydrate addition, or glycosylation, is a post-translational event with considerable microheterogeneity. Three carbohydrate side chains are N-linked to asparagine at the 24, 38, and 83 positions, and one is O-linked to serine at position 126.[10–12]

Early after cloning of the gene, it was appreciated that *in vivo* activity was extremely low in the absence of this post translational glycosylation.[13] Glycosylation required a mammalian system (Chinese hamster ovary) rather than a bacterial or a yeast medium for production of this recombinant glycoprotein. This early recognition of the role of glycosylation for activity of EPO later led to the development of darbepoetin alfa.

EPO is the only true hormonal bone marrow growth factor and is similar structurally to growth hormone. It functions primarily through inhibition of apoptosis[14] rather than as a mitogen, with its primary target cells being late burst-forming unit erythroid (BFU-e) and colony-forming unit erythroid (CFU-e), rather than at the committed stem cell level, binding to cell surface receptors and activating an intracellular phospho-rylation cascade.[15]

rhEPO is available as epoetin alfa and epoetin beta, which differ in their original source of the cloned gene, slightly in their isoforms based on sialic acid content (both also differ in this aspect from native EPO, having higher sialic acid content), and in products stabilizing the final preparations. However, there is no clear superiority of either product's efficacy.

Epoetin alfa is available in the US as Epogen® for use in patients undergoing dialysis and as Procrit® for renal anemia in non-dialysis-dependent patients and in CIA.

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Outside the US, Eprex® is available and is the drug previously implicated in pure red-cell aplasia in a dialysis population in Europe.[16] Epoetin beta is not available in the US; of note, a pegylated form of this drug with a very prolonged half-life is now in early clinical testing.

rhEPO in Oncology

The anemia of chronic renal failure is a pure hormonal deficiency of EPO. As previously noted,[5] cancer-related anemia is due in part to a relative hormonal deficiency, as well as reduced bone marrow responsiveness to EPO, conditions aggravated in the setting of chemotherapy. Trials in this setting were therefore initiated early in the testing phase after rhEPO became available in 1985.[17] Abels'[18] registrational trial led to regulatory approval of epoetin alfa (Procrit®) for use in CIA but not for AoC. Clinical use in the setting of CIA expanded as the open-label trials[19,20] showed quality of life benefit and eventually the feasibility of the more user-friendly once-weekly dosing.[21] While US Food and Drug Administration (FDA) approval was for weight-based dosing of 150 IU/kg thrice-weekly, this 40,000 IU/week fixed dose used in the latter trial escalated by 50% to 60,000 IU/week at week four if less than 1gm/dl increase in hemoglobin is the most frequently employed schedule.

Abels'[18] original trial included one arm with patients not on concomitant chemotherapy, namely patients with the chronic AoC. Early data[17] had suggested that these patients were, if anything, a more responsive group to erythropoietic therapy, as one might predict in the absence of chemotherapy-induced myelosuppression. This thought process presumably led to the failure of this trial to show a reduced transfusion requirement in AoC, and consequentially failure to gain regulatory approval for EPO in this setting. Not only was a smaller dose for epoetin alfa of 100 IU/kg given thrice-weekly chosen but, probably more importantly to the failed trial, patients were only treated for eight weeks as opposed to the 150 IU/kg thrice-weekly for 12 weeks in the two CIA arms. Looking retrospectively, it is now known that this is an inadequate period of time to respond to epoetin alfa. Thus, faulty design in this trial was probably the major factor leading to erythropoietic therapy's never gaining regulatory approval in the US for AoC. However, Compendium® listing does permit reimbursement of this agent in this setting, normally in the same dose schedules employed in CIA.

Darbepoetin Alfa in Cancer

As earlier alluded, the observation that *in vivo* potency of rhEPO was dependent upon post-translational glycosylation led to an exhaustive series of experiments employing site-directed mutagenesis in the development of darbepoetin alfa (Aranesp®). Asparagine was substituted at sites 30 and 88, with three other additional amino acid substitutions also required for proper glycosylation, allowing hyper-glycosylation with five N-linked carbohydrate side chains and increasing the molecular weight to 37,000 daltons and carbohydrate content from approximately 40% to 51%.[22] This hyper-glycosylation resulted in a three-fold greater prolongation of half-life compared with epoetin alfa and a 4.5-fold reduction in binding affinity to the EPO receptor. Both factors, paradoxically in the second instance, increased this compound's *in vivo* biologic activity.

In CIA, this compound has been utilized in weekly and alternate-week regimens with no loss of efficiency or efficacy,[23] and has been shown to effectively treat CIA even when dosed as infrequently as once every three (q 3) weeks.[24,25] There have been no cases of antibodies detected in clinical trials, nor cases of pure red-cell aplasia in patients treated with darbepoetin alfa in renal or cancer settings. Analogous to the dosing with epoetin alfa (Procrit®), the most commonly employed dosing with darbepoetin alfa (Aranesp®) in CIA differs from the FDA-approved weight-based dose of 2.25µg/kg weekly. Rather, fixed dose schedules utilizing a total weekly dose of 100µg and administered every one, two, or three weeks are most frequently employed, also increased by 50% if there is less than a 1gm/dl hemoglobin increase at weeks four to six.

With the theory that darbepoetin alfa's potential for less frequent dosing would be advantageous in patients with chronic anemia of cancer who normally have less frequent office visits, a multicenter trial was undertaken to study this agent in the chronic AoC setting.[6] One hundred and eighty-eight adult patients were included, with hgb <11 who were iron replete, had adequate hepatic and renal function, and received no chemotherapy or radiation therapy within eight weeks of enrollment. Initial cohorts were treated once-weekly for twelve weeks with open label, sequentially escalating doses of 0.5, 1.0, 2.25, and 4.5µg/kg. In a second phase, patients were treated in q 3 and q 4 week schedules, double-blind and placebo-controlled, with a twelve-week optional open label treatment offered to all patients after completing the twelve-week blinded treatment phase. The doses employed in this phase of the trial were 6.75µg/kg q 3 and q 4 weeks and 10µg/kg q 4 weeks. No dose escalation for inadequate response was employed in this trial because of its dose-finding design.

The most frequent diagnosis was breast cancer, but lung, gastrointestinal, gynecologic, genitourinary, and lymphoid malignancies were all well represented. Eighty-three per cent of patients had had prior

Table 1: Hemoglobin End-points and Red Blood Cell Transfusions

	Treatment group – placebo or darbepoetin alfa ($\mu g\ kg^{-1}$)							
	0.5 QW (N=6)	1.0 QW (N=33)	2.25 QW (N=33)	4.5 QW (N=30)	Placebo (N=22)	6.75 Q3W (N=21)	6.75 Q4W (N=21)	10.0 Q4W (N=22)
Hematopoietic response								
Proportion[a]	80	72	70	100	10	60	61	70
(95% CI)	(45, 100)	(55, 89)	(53, 88)	(100, 100)	(0, 24)	(36, 83)	(39, 84)	(50, 91)
Median time to hemato-poietic response (days)	50	50	36	27	NE	57	36	40
Hemoglobin response								
Proportion[a]	80	69	67	92	5	58	49	60
(95% CI)	(45, 100)	(51, 87)	(49, 85)	(80, 100)	(0, 15)	(34, 82)	(26, 73)	(39, 82)
Mean change in hemoglobin concentration (g dl^{-1}) (imputed analysis)[b]								
Mean	1.45	1.66	2.07	2.91	0.00	1.18	1.22	1.70
95% CI	(-0.05,2.95)	(0.90,2.42)	(1.34,2.80)	(2.20, 3.62)	(-0.39,0.39)	(0.33,2.04)	(0.53,1.92)	(0.89,2.50)
Mean change in hemoglobin concentration (g dl^{-1}) (alternate analysis)[b]								
n	4	20	22	18	16	15	15	13
Mean	1.98	2.01	2.69	3.16	0.05	1.71	1.38	2.05
95% CI	(-0.8,4.75)	(0.85,3.18)	(1.83,3.55)	(2.49,3.84)	(-0.40,0.50)	(0.73,2.69)	(0.48,2.28)	(1.5,3.04)
Patients with RBC transfusion from week 5 to EOTP (subset analysis)								
n	5	32	30	29	20	20	20	21
Proportion[a]	20	36	14	7	21	16	6	10
(95% CI)	(0, 55)	(10, 62)	(1, 26)	(0, 17)	(3, 39)	(0, 33)	(0, 16)	(0, 23)

a: Proportion calculated using Kaplan-Meier estimate. b: Change from baseline calculated using last available hemoglobin value not within 28 days of a transfusion (imputed analysis), and for patients with hemoglobin value at week 13 not within 28 days of a transfusion (alternate analysis). QW, once weekly; Q3W, once every three weeks; Q4W, once every four weeks; N, number in cohort; CI, confidence interval; RBC, red blood cell; EOTP, end of treatment period; n, number in subset; NE, not estimable (median not reached).

chemotherapy and/or radiation therapy, with three-quarters of these patients having at least a six-month interval between last treatment and trial entry.

As shown above, 100% of patients achieved a hematopoietic response to the 4.5µ/kg weekly dose (defined as achieving a 2-g hemoglobin increase and/or attaining a hemoglobin of 12g/dl), and all weekly dosages showed a 70% or higher response rate. More important to future usage, in the q3 and q4 week cohorts, responses ranged from 60% to 70%.

Thus, in this study, darbepoetin alfa confirmed what had been expected of erythropoietic therapy in AoC based on early testing of rhEPO shortly after the availability of this agent in the mid 1980s. Namely, this is a condition that is very responsive to erythropoietic therapy, rivaling the response seen in the pure hormonal deficiency state of renal anemia.

The high response rates (up to 100%), rapidity of response (as low as 27 days median time to response), and high mean hemoglobin increase (up to 2.9g/dl

corrected for any transfusion) all show the robust effect of darbepoetin alfa in AoC.

Subsequently, Charu,[26] in a multi-institutional, randomized, open-label trial in AoC, administered darbepoetin alfa every other week and compared it with an untreated control. The 200µg fixed dose every other week had become established as the most commonly utilized dosing schedule with this agent in CIA,[27] and therefore the roughly equivalent 3µg/kg q 2 week dosage was utilized in the 21-week treatment phase of this 25-week trial. Patients were randomized 4:1 to receive darbepoetin alfa 3µg/kg q 2 weeks open-label versus untreated controls who, after twelve weeks, had an optional nine-week treatment at this same dosage. Dose escalations to 5µg/kg q 2 weeks at week seven and 9µg/kg q 2 weeks at week 13 were employed if <1g/dl hemoglobin increase had been achieved.

There was no significant difference in days hospitalized between the treatment and the control groups. However, all other end-points achieved statistical

significance in favor of the darbepoetin–alfa-treated group. Transfusion incidence during weeks five to 12 was 8% versus 22% (p<0.05) in favor of the treated arm. Where a three or greater change in the FACT-Fatigue score is considered clinically meaningful, the treated arm showed a mean improvement of 7.4 versus 1.8 at week nine and 7.7 versus 1.8 at week 13 (p<0.05). Mean hemoglobin increase was 2.1g/dl versus 0.1g/dl in the ITT approach (p<0.001). Hemoglobin response (2g or greater hemoglobin increase) was 68% in treated versus 10% in controls and hematopoietic response (2g/dl hemoglobin increase and/or achieving a hemoglobin of 12) was 76% versus 23% (both with p<0.001).

Based on these results, current recommendation in AoC is for dosing individualized to the patient's given situation. For a patient starting with a hemoglobin of <10 or in the patient with significant symptoms, even if at higher hemoglobin levels, an initial fixed dosage of 200μg q 2 weeks until hemoglobin target is reached would seem appropriate, followed by 500μg q 4 weeks. This would also apply to patient populations less responsive to erythropoietic therapy such as lung cancer and lymphoma. For those patients not requiring as rapid a response, or for patients whose hemoglobin level is above 10 at initiation of treatment, the Smith[6] study suggests that a dosage of 500μg q 4 weeks is an appropriate dose for treatment.

Currently, a phase 3 randomized, double-blind, placebo-controlled multi-institutional study of patients with AoC utilizing darbepoetin alfa 6.75μg/kg q 4 weeks is enrolling patients in a registrational trial. In the trial, the primary end-point is transfusion requirement.

Safety Considerations

Safety considerations must be mentioned, especially in light of the recent events and trials in Europe that have called into question the safety of erythropoietic therapy.[16,28,29] The pure red cell aplasia (PRCA) reported in patients on epoetin alfa (Eprex®) in a dialysis setting[16] has not been reported with any agent in the cancer population. It occurred due to the development of antibodies, which then neutralized native EPO, possibly owing to not employing albumin for stabilization of this product in an attempt to address concerns in Europe of prion-mediated disease transmission. Antibodies to darbepoetin have not been detected in the clinical trial setting, and PRCA has not occurred with darbepoetin in clinical usage.

In the Henke[28] trial, epoetin beta was employed before and during potentially curative radiotherapy in head and neck cancer. The intent was to pre-empt anemia with target hemoglobins of 14g/dl in women and 15g/dl in men. Locoregional control was shortened in the EPO treated arm but interpretation of the trial was confounded by numerous radiation protocol violations and non-random patient drop-outs.

In the BEST[29] trial, epoetin alfa was employed before and during chemotherapy for first-line treatment of metastatic breast cancer. Target hemoglobin was 12-14g/dl. Excessive fatal thrombotic events and deaths due to disease progression in the EPO-treated arm caused early termination of the trial, but the authors again felt that confounding factors make interpretation of the outcomes difficult with regard to a negative EPO effect.

Because of the hypercoagulable syndrome frequently encountered with cancer, there is a relatively high risk of thrombotic events in the oncologic population, with a total incidence of approximately four per 100 patients. Across many studies with all erythropoietic agents, there is an increase in the relative risk (RR) by a factor of approximately 1.5 in the setting of EPO therapy. Trials utilizing EPO in an attempt to pre-emptively prevent anemia, thereby driving hemoglobin levels significantly higher than the usual target hemoglobin of 12g/dl in the treatment of anemia, have had higher thrombotic incidence.[30] This finding stresses the importance of following American Society of Hematology/American Society of Clinical Oncology (ASH/ASCO)[31] and National Comprehensive Cancer Network (NCCN)[32] guidelines when using erythropoietic therapy, certainly in the cancer population. A target hemaglobin level of 12g/dl is appropriate and dose modification by reduced dose and/or frequency of administration is appropriate when this target is attained.

Concern has been voiced due to the presence of the EPO receptor on some tumor cell lines, although the functionality of these receptors is unknown.[33] No evidence suggests that the EPO receptor is an oncogene. There have been no findings from pre-clinical genotoxicity, mutagenicity, or carcinogenicity studies with darbepoetin alfa to suggest promotion of tumor development.[34] Nor is there evidence in animal models or human subjects that elevated EPO levels result in any increased incidence of malignant conditions. In numerous placebo-control studies, there is no shortening of the time-to-progression or any suggestion of a shortened survival in the EPO-treated subjects; in fact, there is a recurring trend in the literature toward improved survival in patients receiving EPO.

Thus, it is important to continue to monitor for safety concerns when employing erythropoietic therapy in the clinical trial setting, but the clinical practitioner should feel no hesitation to utilizing EPO as long as established guidelines are followed.

Future Considerations

Finally, the near future should produce the answer to the question concerning the need and/or route for iron supplementation in oncology patients treated with erythropoietic therapy. Iron supplementation is considered standard, in fact required, in the dialysis patient population with documented improved responsiveness to EPO. The oncologic community has been reluctant to employ intravenous iron supplementation, probably owing to its training background where iron was avoided unless deficiency was documented, avoidance of potential side effects with its administration, and difficulties with reimbursement. Auerbach[35] has published a trial supporting the benefit of intravenous iron and the lack of any benefit with oral iron preparations. A follow-up study is currently being enrolled and should provide the definitive data to resolve this issue.

There has been a relative paucity of studies of concomitant EPO usage in the setting of radiotherapy. The Henke[28] study has made future studies in this area problematic. Nevertheless, there is a clear oxygen enhancement ratio and a nearly uniform adverse impact of anemia on outcome of radiotherapy.[36] Carefully designed and placebo-controlled studies aimed at achieving but not exceeding the previously described hemoglobin target level of 12gm/dl are clearly needed. In all future studies there must be a careful prospective watch for any suggestion of inferior tumor response to treatment, whether these studies are in the chemotherapy, radiation therapy, or combined modality setting. While studies in the chemotherapy setting have tended to support favorable outcomes in patients treated with EPO, and while anemia has normally resulted in inferior outcomes with radiotherapy (not addressing the issue of whether this is causally related or just a surrogate for 'worse' disease), the possibility would certainly exist that this compound's anti-apototic effect might conceivably, though unlikely, serve as a tumor radioprotectant.

Summary

The benefits of EPO therapy in cancer-related anemia are well recognized and documented. Epoetin alfa and darbepoetin alfa are available in the US with no efficacy superiority for either product. However, darbepoetin's flexibility of schedule and route of administration offer obvious advantages to the patient and practitioner. Safety issues have been raised, but if dosed within established guidelines there do not appear to be significant safety concerns that should limit usage in patients, other than possibly in those patients with antecedent thrombotic events. ∎

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