

Prediction of response and other improvements on the limitations of recombinant human erythropoietin therapy in anemic cancer patients

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Background and Objectives. The majority of cancer patients suffer from chronic anemia. While recombinant human erythropoietin (rHuEPO) offers many of the advantages of blood transfusions, response rates to this treatment are variable and in some trials a large proportion of patients (30–50%) did not respond. This failure may be due to factors related to the underlying disease, the chemotherapy given or functional iron deficiency. An accurate means of predicting response to rHuEPO would be beneficial to both healthcare providers and patients.

Evidence and information sources. Data were identified by searches of the published literature, including PubMed, references from relevant reviews, and abstracts presented at recent international oncology and hematology meetings. Only papers in English published between 1990 and 2002 were included. References were selected according to direct relevance to the topic discussed and availability.

State of the art. The best algorithms for predicting response appear to be those combining an assessment of the adequacy of endogenous erythropoietin production together with some early indicators of erythropoietic marrow response. Further characterization of the dose-response relationship of erythropoietic agents may allow better understanding of ways in which response may be enhanced. Adequate iron availability could also contribute to better response rates.

Perspectives. Further characterization of the predictors of response for current and upcoming erythropoietic agents may enhance the management of anemia associated with cancer, and provide more convenient, effective, and flexible therapy.

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Key words: anemia, cancer, erythropoietin, response, iron, darbepoetin α .

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Chronic anemia is a common complication of cancer and its treatment, and occurs in over half of all cancer patients at diagnosis or during the course of the disease.¹ While the incidence of severe anemia in patients with cancer is relatively high in all tumor types, rates are higher among patients with lymphomas, lung tumors or gynecologic tumors (50–60%)² for example, than among those with colorectal or breast cancer (10–20%).³

The etiology of the anemia of cancer is multifactorial, and still not fully understood. Anemia may occur as a consequence of the chronic disease process associated with malignancy, and is therefore often termed anemia of chronic disease (ACD). A shortened red blood cell (RBC) lifespan and failure of the bone marrow to increase RBC production to compensate are believed to be key contributors to the pathogenesis of ACD.⁴ Increased production of inflammatory cytokines has been implicated in suppressing erythropoietic progenitors, blocking storage iron in macrophages and inhibiting the production of erythropoietin (EPO), the primary hematopoietic growth factor.⁵ Anemia may also arise as a result of RBC loss (from hemolysis or bleeding), a reduction in RBC production caused by the cancer (for example, because of bone marrow infiltration, hemophagocytosis or nutritional deficiencies),⁶ or as a side effect of chemo- or radiotherapy.⁷

The clinical manifestations of anemia, which commonly include fatigue, exertional dyspnea, depression, anorexia, indigestion and a reduced skin temperature,³ have traditionally been overlooked or regarded as an inevitable consequence of cancer. However, there is growing recognition that chronic anemia has a significant negative impact on the already impaired quality of life (QOL) of cancer patients. Furthermore, evidence suggests that anemia may be an independent predictor of a poor clinical outcome in cancer patients; it is not known whether this is merely an indicator of more advanced disease or an adverse prognostic factor because it increases tumor resistance to anticancer

therapy.⁸ However, the chronic anemia that is so frequently associated with cancer may be not only treatable, but also, to some extent, preventable with erythropoiesis-stimulating proteins.^{9–11}

Current therapy for anemia includes RBC transfusions and recombinant human erythropoietin (rHuEPO). rHuEPO is invaluable in raising hemoglobin (Hb) levels and improving QOL. However, this therapy has a number of limitations, which will be discussed in this paper. One of the limitations of rHuEPO — the failure of a substantial proportion of patients to respond to standard doses — will be explored in detail together with the value of identifying predictive factors for response to rHuEPO. Further approaches to enhance the current management of anemia, such as iron supplementation and modified schedules of administration (including those allowed by the new erythropoietic protein, darbepoetin α) are also discussed.

Factors influencing the risk of cancer-associated anemia and transfusions

Clearly, it would be of great benefit to be able to predict which patients are most likely to develop anemia, particularly those undergoing chemotherapy or radiotherapy, as the incidence of anemia is high among this group.^{2,12} The likelihood of a patient who is receiving chemotherapy developing anemia depends on several factors, including the type, schedule and intensity of therapy.² For example, platinum-based chemotherapy, which forms the basis of first-line therapy for lung and ovarian cancer, is particularly myelotoxic, and produces severe anemia in up to 23% of patients with lung cancer, and in up to 42% of patients with ovarian cancer.² In contrast, newer agents such as the taxanes (paclitaxel and docetaxel), vinorelbine and gemcitabine are associated with higher incidences of mild-to-moderate anemia and lower incidences of severe anemia in patients with lung cancer.

Several researchers have identified factors that may predispose patients to developing anemia, primarily severe anemia requiring transfusion, which are listed in Table 1.^{13–20} Ray-Cocquard *et al.*¹⁷ have developed the only predictive algorithm to date, a risk model that estimates the likelihood of developing severe anemia requiring transfusion within 31 days of starting chemotherapy. This algorithm requires the calculation of a Risk Index Score according to the presence of three factors: performance status >1 ; day-1 (of chemotherapy) lymphocyte count $\leq 700/\mu\text{L}$; and day-1 Hb level of <12 g/dL.¹⁷ The presence of each of the first two factors receives a score of 1 each, while a low baseline Hb

Table 1. Factors that may be predictive of the development of anemia in patients with cancer.

Possible predictive factor

Cytotoxic chemotherapy
- cisplatin-containing ^{14,15}
- higher dose ¹⁴
- etoposide or 5-fluorouracil ¹⁵
- carboplatin- versus cisplatin-containing ¹⁸
- higher ultrafilterable platinum concentration ¹⁹
Low baseline Hb level ^{13,14,16,18–20}
Performance status >1 ¹⁷
Lymphocyte count $\leq 700/\text{mL}$ on day 1 of chemotherapy ¹⁷
Decrease in Hb level during first month of therapy ¹⁶
Particular tumor types
Hodgkin's disease ¹⁶
non-Hodgkin's lymphoma ¹⁶
ovarian cancer ^{13, 16}
lung cancer ^{13,20}
leukemia ²⁰
History of prior transfusions ¹⁶
Longer duration of chemotherapy ¹⁶
Metastatic disease ¹³

Hb: hemoglobin.

Table 2. Probability of developing severe anemia requiring RBC transfusion within 31 days after starting chemotherapy, according to the Risk Index Score (see text for calculation of Risk Index Score).¹⁷

Risk Index Score	Calculated probability of receiving RBC transfusion	
	%	95% CI
≥ 4	30	16–47
2 or 3	11.4	7–18
1	3.8	3–5
0	1.2	1–2

RBC: red blood cell; CI: confidence interval.

level receives a score of 3. The individual scores are added (giving a maximum of 5), and the probability of developing severe anemia requiring transfusion within 31 days after the start of chemotherapy for each total score is determined using the values given in Table 2.

While several investigations have identified possible predictive factors, many studies have been limited by their retrospective nature, which has restricted analysis to only those measurements that were taken as part of routine care. Consequently, few studies examine the same potential predictive factors, making it difficult to draw conclusions. In addition, while some investigators found evidence of an association between particular risk factors

and anemia, others specifically noted no association for these factors.

However, although no factor besides low baseline Hb levels has consistently been associated with an increased risk of developing anemia during the course of treatment, physicians would be well advised to consider whether each individual patient possesses any number of the risk factors identified. Certainly, low baseline Hb appears to be a strong indicator of the likelihood of anemia worsening during therapy, and certain tumor types (for example, hematologic, lung or ovarian) and chemotherapy regimens (for example, cisplatin-containing) are more likely than others to be associated with the development of anemia.

Management of cancer-associated anemia

At present, two principal options are available for the management of chronic anemia in patients with cancer: blood transfusions and treatment with rHuEPO. Blood transfusions have traditionally been given when severe anemia (Hb <8 g/dL) develops,²¹ and rapid relief of anemia is required. The decision to treat with rHuEPO is usually determined by patients' Hb levels and symptoms; rHuEPO has generally been given to patients when their Hb levels have dropped to <10 g/dL. With increasing recognition that treatment of even mild-to-moderate anemia (Hb levels approximately 8-12 g/dL) can lead to a significant improvement in QOL,²² rHuEPO therapy is now being considered for higher Hb levels, as dictated by symptoms.

Blood transfusions

Despite significant advances in this area, conventional red blood cell transfusions are still associated with a number of serious risks that must be taken into account in any treatment decision, although the odds of developing these complications are minimal. These include risks of transmission of viral or bacterial infections;²³ pulmonary edema; hemolytic reactions; allergic reactions to donor proteins; progressive iron overload; and alloimmunization to RBC and platelet antigens.^{23,24} The inconvenience to patients, and the time and financial costs incurred by hospitals and clinics, are further disincentives for the use of blood transfusions in the routine management of cancer-associated anemia.³ It must be noted, however, that in chronically and terminally ill patients, the hazards associated with transfusions may be of little or no consequence given that the patients' lifespan may already be substantially reduced.

Treatment with rHuEPO

The ability of rHuEPO to correct cancer-associated anemia was first demonstrated in patients with low-grade lymphoma or multiple myeloma, all of whom were anemic as a consequence of the underlying disease.²⁵ Further studies have confirmed and expanded these early findings, demonstrating that treatment with rHuEPO raises Hb levels, reduces the need for RBC transfusions, and improves QOL.^{22,26-35} rHuEPO is also effective when administered prophylactically to prevent or postpone the onset of chemotherapy- or radiotherapy-induced anemia.^{9,10,36}

Limitations of rHuEPO treatment

Clinical trials have demonstrated that rHuEPO provides many of the benefits of blood transfusions - albeit significantly more slowly - without the risks associated with the transfusion of allogeneic blood. Nevertheless, despite the proven safety and efficacy of rHuEPO in correcting cancer-related anemia in a significant proportion of patients, therapeutic response rates vary markedly among patients receiving treatment, and in some trials, as many as 40-50% of patients with cancer-associated anemia failed to derive any clinical benefit from rHuEPO.^{22,26,29,30} The median time to response (Hb increment >2 g/dL) is approximately 6 to 10 weeks in patients with myeloid or lymphoproliferative malignancies,^{34,35,37-39} approximately 7 weeks in patients with nonmyeloid malignancies,²² and occasionally up to 12 weeks are needed to rule out unresponsiveness in an individual patient.⁴⁰

Factors contributing to failure of rHuEPO treatment

Despite the fairly high proportion of patients who do not respond to rHuEPO, relatively little is known about the causes of this treatment failure. Several disease- and treatment-related factors have been identified that may reduce a patient's response to rHuEPO treatment (Table 3). Although most of these were identified in patients with chronic kidney disease, they are also likely to apply to patients with cancer.

Of these factors, functional iron deficiency is likely to be one of the most significant and common contributing factors. This is defined as an iron deficit in the functional erythroid compartment, and is the result of an imbalance between iron needs in the erythroid marrow and iron supply. This may occur even in the presence of large iron stores (increased ferritin) when the release of stored iron is inadequate.⁶ Although the vast majority of patients with chronic kidney disease treated with

Table 3. Factors limiting the efficacy of rHuEPO therapy.

Factor
Functional iron deficiency
Inflammation
Infection
Surgery
Bleeding
Hemolysis
Folate or vitamin B ₁₂ deficiency
Massive marrow infiltration
Extensive stem cell damage
Marrow fibrosis
Intensive chemotherapy
Hemophagocytosis

rHuEPO develop functional iron deficiency that seriously limits their erythropoietic response,⁴¹ this has not been specifically examined in cancer patients. However, there is every reason to believe that its prevalence is also very high in this setting. Functional iron deficiency is best diagnosed by a transferrin saturation level below 20% or a fraction of hypochromic red cells greater than 10%.

Inflammation (and its accompanying pro-inflammatory cytokines), infections, hemorrhage and complications of chemotherapy may also have a profound negative impact on response to rHuEPO treatment.⁴² Surgery is often followed by a transient loss of response to rHuEPO, not only because of blood loss, but also because iron reutilization is impaired post-operatively.⁴³ Blood loss and hemolysis, while not directly reducing the erythropoietic effect of rHuEPO, may be manifested as an apparently poor response to rHuEPO because of increased RBC losses.⁴⁴

Although vitamin B₁₂ and folate deficiencies are less common than deficiency of iron, they may contribute to a poor response to rHuEPO, as both are essential for RBC development.⁴⁴ Vitamin B₁₂ and/or folate deficiencies are likely to be more common in patients with gastrointestinal malignancies, in which malabsorption secondary to surgical resection may occur.

Bone marrow metastases may impair response to rHuEPO in cases in which there is major invasion by cancer cells and limited residual normal hematopoiesis, however, bone marrow involvement does not otherwise appear to affect the efficacy of treatment with rHuEPO.^{25,32} In addition, conditions causing inherent disorders of erythropoiesis (for example, myelodysplastic syndrome, aplastic anemia or some of the hemoglobinopathies) may

reduce the effectiveness of rHuEPO, with some patients showing a profound resistance to rHuEPO, even at high doses.⁴⁴

In addition, chemotherapy may affect the body's ability to respond to rHuEPO. More intensive chemotherapy regimens are associated with lower rates of response to rHuEPO, the extreme example being autologous bone marrow transplantation in which rHuEPO therapy is not efficient in the early post-transplant period.⁴⁵ However, patients receiving chemotherapy of moderate intensity respond as well to rHuEPO as those not receiving concomitant chemotherapy,³² and there is no marked difference between those receiving platinum-based regimens and those receiving other forms of chemotherapy.^{31,32}

The type of tumor does not generally appear to affect response rate,³² although small studies have suggested that patients with breast or colon cancer may derive less benefit from rHuEPO than those with myeloma.⁴⁶ A meta-analysis has produced similar findings, reporting higher response rates in patients with multiple myeloma compared with other types of cancer.⁴⁷ However, these differences may also reflect variations in the myelosuppressive effects of the various forms of chemotherapy.

Improvements in erythropoietic therapy

Predicting response to rHuEPO

Considering the wide variation in the response of cancer patients to rHuEPO, the development of an algorithm to facilitate accurate identification of those patients who are more likely to demonstrate an adequate treatment response would be extremely valuable. Ideally, this would enable the targeting of therapy to those patients who would benefit significantly from this treatment approach, thus minimizing the risk of prolonged treatment without clinical benefits.

A predictive algorithm of response to rHuEPO was first proposed in the setting of the anemia associated with renal failure.⁴⁸ Sixty-four consecutive unselected hemodialysis patients received intravenous rHuEPO three times weekly, at a starting dose of 50 U/kg, which was increased to 75 and 100 U/kg if no response was observed after 1 and 2 months of treatment, respectively. The value of various laboratory parameters (including baseline values and early changes) as predictors of response to rHuEPO were analyzed retrospectively. Using various statistical methods, the investigators found that baseline fibrinogen (an indicator of inflammation) and serum soluble transferrin receptor (sTfR; a marker of functional iron deficiency), as

Table 4. Prediction of response to rHuEPO in hemodialysis patients using baseline levels of sTfR and fibrinogen, with or without 2-week sTfR increment.⁴⁸

2-week sTfR increment (%)	Baseline level of sTfR (ng/mL)	Baseline level of fibrinogen (g/L)	Response rate (%)
Model 1: using baseline parameters only			
-	<3,500	<4	100
-	≥3,500	<4	67
-	<3,500	≥4	67
-	≥3,500	≥4	29
Model 2: including 2-week sTfR increment			
≥20	-	-	96
<20	<3,500	<4	100
<20	<3,500	≥4	12
<20	≥3,500	<4	62

well as the early sTfR increment (a quantitative measure of erythropoietic activity), were the most useful predictors of response to rHuEPO. When only pretreatment parameters were used in the predictive model, a 100% response rate was observed when sTfR and fibrinogen were both low, whereas when both variables were high the response rate was 29% (Table 4). In the second predictive model used, the increment in sTfR over the first 2 weeks of treatment was also included. When the 2-week sTfR increment was over 20%, or when both baseline sTfR and fibrinogen were low, response rates of greater than 95% were observed. In contrast, virtually no response was observed when the sTfR increment was low and baseline fibrinogen was elevated (Table 4). These predictive factors illustrate the importance of the early erythropoietic response (changes in sTfR levels), subclinical inflammation (fibrinogen) and functional iron deficiency (baseline sTfR).

Ludwig *et al.*³⁷ conducted an in-depth investigation of the prognostic significance of 21 different hematologic and humoral variables in patients with chronic anemia of cancer. Eighty patients, six of whom received chemotherapy and one of whom was irradiated during the first 2 weeks of rHuEPO treatment, were given rHuEPO at an initial dose of 150 U/kg three times weekly. Patients not responding with an increase in Hb of ≥2 g/dL after 6 weeks of treatment had their rHuEPO dose increased to 300 U/kg. Of the 80 patients, 37 had hematologic malignancies and 43 had solid tumors. Multivariate discriminant analysis and logistic regression analyses of response were performed on the results

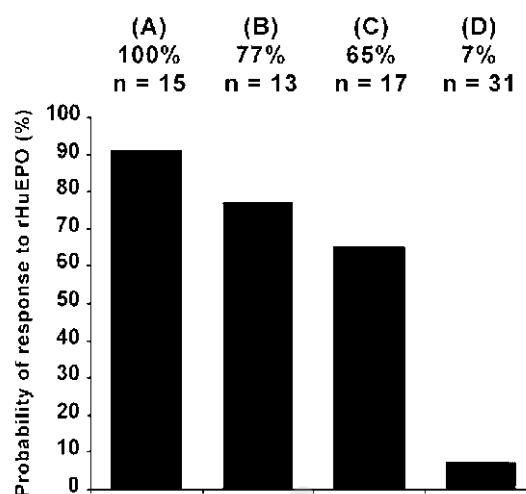


Figure 1. Prediction of response to rHuEPO in anemia of cancer patients using the 2-week absolute serum EPO level and the Hb increment.³⁷ (Ludwig H, personal communication 2001). (A) 2-week serum EPO <100 mU/mL and Hb increment >0.5 g/dL, n = 15; (B) 2-week serum EPO <100 mU/mL and Hb increment <0.5 g/dL, n = 13; (C) 2-week serum EPO >100 mU/mL and Hb increment >0.5 g/dL, n = 17; (D) 2-week serum EPO >100 mU/mL and Hb increment <0.5 g/dL, n = 31.

of routine blood tests from the 76 patients who received rHuEPO for at least 2 weeks in an attempt to identify potential response predictors. None of the baseline variables, which included concentrations of Hb, reticulocytes, sTfR, EPO, ferritin, transferrin, platelets and several cytokines and acute-phase proteins, were sufficiently strongly associated with response to rHuEPO treatment to serve as a reliable prognostic indicator. On the other hand, data collected after 2 weeks of treatment proved more useful. The algorithm developed from this study is shown in Figure 1, and offers two options. Firstly, if after 2 weeks of therapy, serum erythropoietin is >100 mU/mL and Hb concentration has increased by <0.5 g/dL, it is very likely the patient will not respond to rHuEPO (predictive power 93%).³⁷ Of the patients who do not fulfill these criteria, response can be predicted with an accuracy of 80%. Among such patients, if the serum erythropoietin level is <100 mU/mL and the Hb concentration has increased by >0.5 g/dL, the probability of response to rHuEPO is very high (accuracy 95%). For the others (30 of the 76 patients), the mean response rate was approximately 70%. If the first option cannot be used (for example, the required laboratory measurements cannot be

obtained), a serum ferritin level of ≥ 400 ng/mL after 2 weeks of rHuEPO therapy strongly indicates unresponsiveness (predictive power 88%). In contrast, a serum ferritin level of < 400 ng/mL suggests response in three out of four patients.

In a subset of patients with hematologic malignancies or solid tumors from a large multicenter study, some prediction of response could be derived from changes observed in reticulocytes and Hb from baseline to week 2 of therapy.⁴⁹ Patients receiving chemotherapy ($n = 132$) were given rHuEPO at 150 U/kg or placebo subcutaneously three times weekly for 12 weeks, while another set of patients not receiving chemotherapy ($n=54$) was given rHuEPO at 100 U/kg or placebo subcutaneously three times weekly for up to 8 weeks. Overall, 54% of patients receiving chemotherapy responded to rHuEPO with an increase in Hb of ≥ 2 g/dL, while only 32% of patients not receiving chemotherapy responded. Patients were retrospectively stratified by changes in Hb and absolute reticulocyte count at weeks 2 and 4. Among patients not receiving chemotherapy (Figure 2A), the response rate was poor when the 2-week increment of the Hb level was < 0.5 g/dL (7%), but it was greatly improved when the Hb level and reticulocyte count increased by ≥ 0.5 g/dL and $\geq 40,000/\mu\text{L}$, respectively (91%).⁴⁹ The predictive power of these parameters was much less substantial when Hb increased by ≥ 0.5 g/dL and the reticulocyte elevation was $< 40,000/\mu\text{L}$ (a 36% response rate). In contrast, adequate prediction of response could not be provided on the basis of Hb and reticulocyte changes in patients receiving concomitant chemotherapy (Figure 2B).⁴⁹ Although some improvement in prediction could be obtained in patients increasing their Hb by ≥ 1 g/dL after 4 weeks of treatment, predicting response on the basis of the response itself may appear to be trivial.

Theoretically, patients with defective endogenous EPO production would be more likely to respond to rHuEPO than those with adequate serum EPO levels. In a study by Osterborg *et al.*,³⁵ patients with anemia associated with multiple myeloma or low-grade non-Hodgkin's lymphoma (NHL) (of whom 88% received chemotherapy throughout the study) were randomized to receive subcutaneous rHuEPO at a fixed dosage (10,000 U/day) or at a titrated dosage (2,000 U/day for 8 weeks, then increased in a stepwise manner to 10,000 U/day). The presence of a deficiency of EPO relative to the degree of anemia (a *relative EPO deficiency*) was analyzed in each patient prior to the initiation of therapy by calculating the ratio between observed (O) and predicted (P) baseline serum EPO concentrations: the

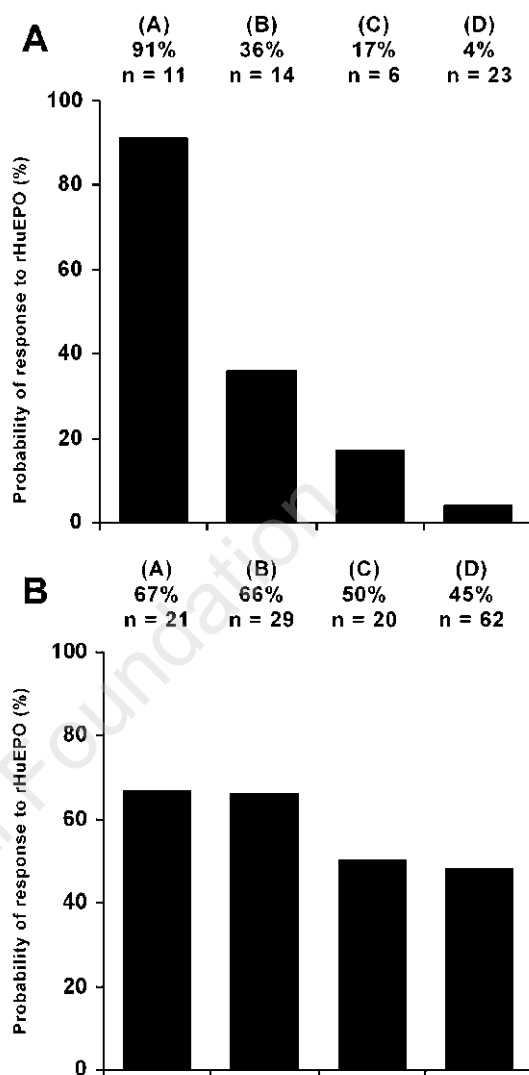


Figure 2. Prediction of response to rHuEPO in anemia of cancer patients using the 2-week Hb and reticulocyte increments.⁴⁹ A good prediction can be obtained in patients not receiving chemotherapy, $n = 54$ (Figure 2A), but not in those receiving chemotherapy, $n = 132$ (Figure 2B). (A) 2-week Hb increment ≥ 0.5 g/dL and reticulocyte increment $\geq 40,000/\mu\text{L}$; (B) 2-week Hb increment ≥ 0.5 g/dL and reticulocyte increment $< 40,000/\mu\text{L}$; (C) 2-week Hb increment < 0.5 g/dL and reticulocyte increment $\geq 40,000/\mu\text{L}$; (D) 2-week Hb increment < 0.5 g/dL and reticulocyte increment $< 40,000/\mu\text{L}$.

O/P EPO ratio. rHuEPO appeared most effective in those patients with a deficiency in EPO relative to the degree of anemia (O/P EPO ratio < 0.9), and patients with an O/P EPO ratio of < 0.6 had a very high response rate (89%). Unresponsiveness to rHuEPO could be predicted with a high probability, as the response rate among patients with an

O/P EPO ratio ≥ 1.2 was only 10%. As it was felt that in clinical practice it would be more useful to relate the (uncorrected) serum EPO concentrations to the probability of response, the investigators also assessed the predictive value of observed EPO concentrations. Using cut-off values of 50 mU/mL and 400 mU/mL, a baseline serum EPO concentration of < 50 mU/mL was found to be associated with a response rate of $> 76\%$, whereas a value ≥ 400 mU/mL strongly predicted non-response (cumulative response rate 9%). Multivariate analysis confirmed that relative EPO deficiency (low O/P EPO ratio) was the most important factor in determining response to rHuEPO. A decreased platelet count ($< 100 \times 10^9/L$) was also associated with a lower probability of response.

In patients with hematologic malignancies, low baseline serum EPO levels or a decreased O/P EPO ratio were associated with a significantly higher probability of response.^{34,35,37-39} In contrast, studies in patients with solid tumors have failed to confirm this observation. However, this may be the result of inadequate timing of serum EPO sampling; indeed, serum EPO should be evaluated just prior to chemotherapy because decreased EPO utilization by target cells causes inappropriately elevated serum EPO levels in the 2 weeks after chemotherapy.⁵⁰

A combination of baseline parameters and early changes observed after 2 weeks of rHuEPO therapy may provide another useful approach.³⁴ Patients with multiple myeloma or non-Hodgkin's lymphoma, of whom 79% received chemotherapy during the study, were randomized to receive 8 weeks of therapy with subcutaneous rHuEPO at doses ranging from 1000 to 10,000 U/day. Seventy-seven percent of patients had an inadequate production of endogenous EPO, as judged by an O/P EPO ratio of ≤ 0.9 . The authors performed regression analysis, using a Cox's proportional hazard model, and classification and regression tree analysis to identify the most important factors predicting response in patients receiving 5000 and 10,000 U of rHuEPO daily. The failure rate was high when the baseline serum O/P EPO ratio was higher than 0.9 (87%), or when the baseline serum O/P EPO ratio was less than 0.9 and the 2-week Hb increment was < 0.3 g/dL (100%) (Figure 3).³⁴ On the other hand, the success rate was 88% when the baseline serum O/P EPO ratio was less than 0.9 and Hb increased by ≥ 0.3 g/dL. A baseline serum EPO concentration of ≤ 50 mU/mL in combination with the 2-week change in Hb of ≥ 0.3 g/dL was also found to predict success with an accuracy of around 90%.

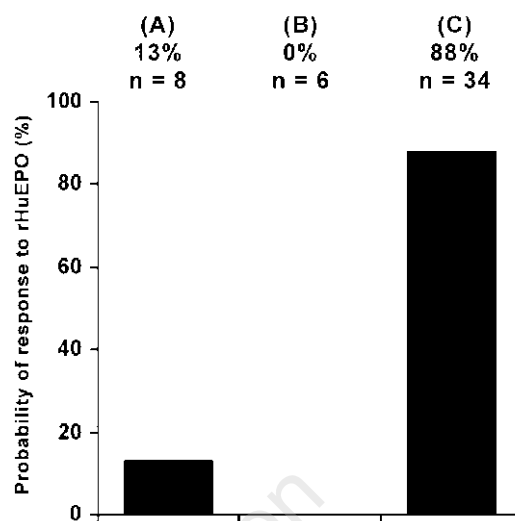


Figure 3. Prediction of response to rHuEPO in anemic patients with NHL or multiple myeloma using the baseline serum O/P EPO ratio and the 2-week Hb increment.³⁴ (A) Baseline O/P serum EPO > 0.9 , n = 8; (B) Baseline O/P serum EPO < 0.9 and Hb increment < 0.3 g/dL, n = 6; (C) Baseline O/P EPO < 0.9 and Hb increment ≥ 0.3 g/dL, n = 34.

The potential value of the combination of baseline parameters and changes in indicators of erythropoietic activity was demonstrated in another single-center study.³⁹ Fifty-eight anemic patients with hematologic malignancies (n = 38) and solid tumors (n = 20) received a starting dose of 375 U/kg/week rHuEPO, administered subcutaneously once daily, for 5 days per week. Patients who did not respond (response was defined as an increase in Hb of ≥ 2 g/dL in the absence of a red blood cell transfusion) after 4 weeks of therapy had their dose increased to 750 U/kg/week for another 4 weeks. The value of a variety of laboratory parameters (baseline levels, 2-week and 4-week changes) was studied using multiple regression analysis. An inverse relationship between the 8-week (end of study) change in Hb and the baseline serum O/P EPO ratio ($p < 0.001$) was noted; however, absolute baseline serum EPO and sTfR increments after 2 weeks were found to be the most useful variables when developing a predictive algorithm. Only 18% of patients with a baseline serum EPO > 100 mU/mL responded to treatment, and only 29% of patients responded when the baseline serum EPO was < 100 mU/mL but the 2-week sTfR increment was $< 25\%$ (Figure 4). On the other hand, the response rate was 96% among patients with a low baseline serum EPO and sTfR elevation of $\geq 25\%$.

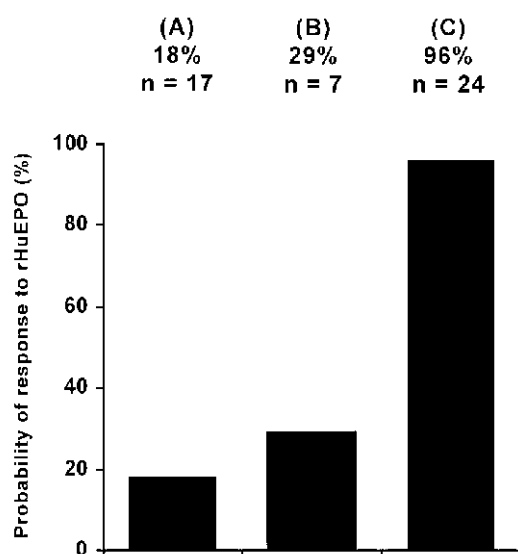


Figure 4. Prediction of response to rHuEPO in anemia of cancer patients using the baseline serum EPO level and the 2-week sTfR increment.³⁹ (A) Baseline EPO >100 mU/mL, n = 17; (B) Baseline EPO <100 mU/mL and sTfR increment <25%, n = 7; (C) Baseline EPO <100 mU/mL and sTfR increment ≥25%, n = 24.

Thus, retrospective studies have shown that it may be possible to predict, soon after initiating therapy with rHuEPO, which patients with cancer-associated anemia are likely to benefit from this particular treatment approach. Several algorithms have been proposed; their sensitivity (how well the algorithm identifies all those who will respond) and specificity (how well the algorithm excludes all those who will fail), and thus their overall efficacy, vary. The positive predictive value (probability of response in those predicted to respond) of the algorithms is usually better than their negative predictive value (probability of failure in those predicted to fail). The best algorithms appear to be those combining an assessment of the adequacy of endogenous EPO production together with some early indicators of erythropoietic marrow response, such as the 2-week increment of sTfR or Hb.

There are some theoretical reasons why some or all of these parameters might not be of value in certain situations. Whereas low baseline serum EPO levels or inadequate O/P ratios were associated with a significantly higher probability of response in patients with hematologic malignancies, this was not usually the case in patients with solid tumors. On the other hand, Hb increments after 2 weeks of treatment may be of value in patients whose Hb levels are in a steady state, but are of lit-

tle help in transfused patients and in those in whom rHuEPO is intended to prevent the occurrence of severe anemia.⁵¹ Changes in reticulocyte counts may simply reflect the output of shift reticulocytes and not a true expansion of erythropoiesis, and often have not been found to be a good indicator of response. Finally, although sTfR levels represent the best quantitative measurement of total erythropoietic activity, they may also increase slightly, secondary to functional iron deficiency.

It should be emphasized that the various algorithms described here address very similar predictors of response. Specifically, they all examine the appropriateness of baseline endogenous EPO production and/or early indicators of erythropoietic marrow response to rHuEPO. In practise, the following scheme could be adopted: serum EPO should be measured at baseline in patients with hematologic malignancies and treatment with rHuEPO not initiated if endogenous serum EPO is >100 mU/mL (or >200 mU/mL in severely anemic patients) or the O/P ratio is >0.9. Erythropoietic response should be assessed after 2 weeks. In non-transfused patients, if Hb has increased by at least 0.3 g/dL, rHuEPO treatment should be continued. If the Hb level has not increased, the rHuEPO dosage should be doubled and Hb measured again after a further 2 weeks of treatment; if Hb has not increased by >0.3 g/dL after the additional 2 weeks, rHuEPO should be discontinued. In transfused patients, if sTfR has increased by at least 20%, rHuEPO treatment should be continued. If not, the rHuEPO dosage should be doubled and sTfR measured again 2 weeks later. If sTfR has not increased by at least 20% after the additional 2 weeks, rHuEPO should be discontinued. It is, of course, critical that all preventable causes of rHuEPO failure are identified prospectively and corrected, or else no predictive model will be valid. In particular, this includes ensuring adequate iron supply and energetic treatment of intercurrent complications, such as infections and bleeding.

Therefore, while the various predictive algorithms are promising, they require further refinement as well as confirmation and comparison in a larger number of patients. It is hoped that such algorithms may help to ensure a more targeted approach to the use of rHuEPO in the setting of the chronic anemia of cancer. By administering rHuEPO and related products specifically to those patients who have a high likelihood of responding to treatment, the cost effectiveness of these medications can be optimized to the advantage of both patients and healthcare providers.

Iron supplementation

Owing to the increased erythropoietic activity stimulated by rHuEPO, adequate delivery of iron to the bone marrow is an important consideration in all clinical situations in which rHuEPO is used, including cancer (the relationship between rHuEPO, iron and erythropoiesis has been reviewed by Goodnough *et al.*⁵²). Functional iron deficiency is a very frequent limitation of rHuEPO therapy. However, because there is some concern that tumor cells require iron for optimal growth,⁵³ routine iron supplementation for all cancer patients receiving rHuEPO is not recommended. The same is true for both oral and intravenous iron supplementation. However, this should be balanced with the fact that transfusion of one RBC unit also provides a large amount (200 mg) of iron.

Iron supplements should be given when absolute iron deficiency is suspected, i.e. when serum ferritin is 40–100 µg/L, a level associated with absence of iron stores in ACD.^{4,24} Otherwise, iron supplements should be given in the case of functional iron deficiency, i.e. when the transferrin saturation is below 20% or the percentage of hypochromic RBCs is greater than 10%, and may be discontinued when they stabilize within the normal range. The experience in iron-replete renal failure patients has clearly indicated that oral iron supplementation is only marginally superior to no iron but that intravenous iron both substantially improves response when rHuEPO therapy is initiated⁵⁴ and allows considerable reduction (in the order of 40%) of rHuEPO dose requirements during the maintenance phase.⁵⁵ The safety profile of iron saccharate, an iron complex taken up by reticuloendothelial cells, makes it the preferred intravenous compound over iron dextran (more anaphylactic reactions) or iron gluconate (more toxicity owing to free iron release).^{56,57} According to the manufacturers' recommendations, the maximum doses are 1000 mg for iron dextran, 500 mg for iron saccharate and 62.5 mg for iron gluconate.⁵⁸

Iron usage has not been energetically pursued in clinical trials of rHuEPO in cancer patients and was generally left to the discretion of the individual investigator. This was based on the false perception that cancer patients do not have decreased iron stores (ferritin) and thus, do not require iron supplementation with rHuEPO therapy. In addition, iron has only been given orally, a method proven to be of little efficacy in renal failure patients and presumably even less effective in cancer patients because of impaired iron absorption, another characteristic of ACD.^{4,24} The efficacy of intravenous iron

to correct functional iron deficiency and improve anemia has been well documented in rheumatoid arthritis during rHuEPO therapy⁵⁹ and after failure of oral iron in juvenile chronic arthritis,⁶⁰ two diseases also associated with ACD. Apart from anecdotal reports on the efficacy of intravenous iron in patients failing to respond to rHuEPO, iron supplementation has not been formally studied in the anemia of cancer. Probably, intravenous administration of 100–300 mg iron saccharate every week or every other week will ensure the best utilization of any given dose of rHuEPO. Future clinical trials are required to investigate the safety and efficacy of intravenous iron in cancer patients treated with rHuEPO.

Administration and dose-response relationship of rHuEPO

Several studies have suggested that raising the dose of erythropoietic agents may increase response rates if an inadequate response is seen shortly after commencement of therapy,^{22,28,35} indicating that an understanding of the dose–response relationship of these agents is desirable. In a large, open-label trial involving 2,370 patients with non-myeloid malignancies, Demetri *et al.*²² reported that patients whose Hb levels did not increase by ≥ 1 g/dL after 4 weeks of rHuEPO therapy received a doubled dose of rHuEPO (from 10,000 to 20,000 U three times weekly), and of these, 44% went on to achieve either a Hb increase of ≥ 2 g/dL or a Hb level of ≥ 12 g/dL by the end of the study. Similarly, in the study by Osterborg *et al.*, patients had their rHuEPO dose titrated from 2,000 U/day to 5,000 U/day if Hb had not reached 11 g/dL after 8 weeks of therapy after eliminating the need for transfusions, and then to 10,000 U/day if Hb had not reached 11 g/dL by 12 weeks after eliminating the need for transfusions.³⁵ Fourteen percent of patients receiving 2,000 U/day responded to rHuEPO therapy, and after stepwise escalation to 5,000 U and 10,000 U daily, the cumulative response rate increased to 42% and 60%, respectively.

Reflecting the potential value of dose increases, the approved dosing schedule for rHuEPO (three times weekly by subcutaneous injection) includes a dose-escalation for inadequate response. Using the approved three-times-weekly dosing frequency, patients who are suitable for rHuEPO therapy receive a starting rHuEPO dose of 150 U/kg. If an inadequate hematopoietic response is observed after 1 month of therapy (Hb increase < 1 g/dL), the dose can be doubled to 300 U/kg three times weekly. Since it is unlikely that patients who do not

respond to 300 U/kg will respond to higher doses of rHuEPO, therapy can be discontinued in non-responding patients after 8 weeks of therapy. If Hb levels rise to >13 g/dL, therapy should be discontinued, but resumed at 75% of the previous dose until Hb has dropped to ≤ 12 g/dL.

While the currently approved dosing schedule is three times weekly, recent data from an open-label, multicenter trial involving 3,012 anemic patients with non-myeloid malignancies who were receiving chemotherapy suggest that once-weekly dosing of rHuEPO is also feasible,²⁸ and in fact a once-weekly dosing schedule is common practice in the United States. The trial by Gabilove *et al.*²⁸ indicated that dose increases on a once-weekly schedule were well tolerated and were associated with an increase in response rates; however, longer intervals between dosing may have a negative impact on patient compliance as infrequent injections are difficult to remember. Patients initially received 40,000 U rHuEPO once weekly by subcutaneous injection, and those whose Hb increased by < 1 g/dL after 4 weeks of therapy had their rHuEPO dose increased to 60,000 U/week. The hematopoietic response rate to 40,000 U rHuEPO once weekly was 49%, and this rose to 68% when patients who required dose escalation had their rHuEPO dose increased (33% of patients during the 16-week study). In this trial, hematopoietic response was defined as an increase in Hb of ≥ 2 g/dL or achievement of a Hb level of ≥ 12 g/dL, with no transfusions in the previous 30 days. The feasibility of once-weekly subcutaneous dosing in patients with lymphoproliferative malignancies has also been demonstrated.⁶¹ Patients received either rHuEPO 30,000 U/week or rHuEPO 10,000 U three times weekly, with a dose increase to 60,000 U weekly if Hb increased by <0.5 g/dL by week 5 and/or patients required a RBC transfusion during week 4. Response to rHuEPO (Hb increase ≥ 2 g/dL from baseline and no transfusions in the 6 weeks before the last available Hb value) was similar in both groups, at 72% and 75% for the once-weekly and three-times-weekly schedules, respectively.

Despite the many trials in which patients received a dose escalation, the precise dose-response relationship for rHuEPO has not been extensively evaluated, which may be inhibiting further dose optimization. It is likely, however, that there is a certain point beyond which the erythroid marrow will be unresponsive to further increases in rHuEPO dose.

Darbepoetin α

Further improvement on the EPO molecule may arise from the development of darbepoetin α (ARANESP™, Amgen Inc., Thousand Oaks, CA, USA), a unique erythropoiesis stimulating protein. Darbepoetin α is an erythropoietic protein that is similar to EPO but has a higher sialic acid content than endogenous EPO and rHuEPO, and a longer half-life and greater biological activity than rHuEPO. In addition to exploring the safety and efficacy of this agent when given at less-frequent dosing intervals than rHuEPO, clinical trials are underway to fully characterize the dose-response relationship.

A large phase I/II clinical trial, involving anemic patients with solid tumors receiving concurrent chemotherapy, exploring the dose-response relationship of darbepoetin α , has indicated that the higher the dose, the faster the response and the greater the proportion of responders.^{62,63} In Part A of this study, 60 patients were randomized to receive rHuEPO (150–300 U/kg) and 228 to receive darbepoetin α (1.5, 2.25, 4.5 $\mu\text{g}/\text{kg}/\text{week}$, among other doses). Hematopoietic response rates (Hb ≥ 12 g/dL or ≥ 2 g/dL increase in Hb from baseline) ranged from 53% (95% CI: 37,71) to 84% (95% CI: 70,98) for darbepoetin α doses from 1.5 to 4.5 $\mu\text{g}/\text{kg}/\text{week}$. In Part B of this study, in which 35 patients were randomized to rHuEPO (40,000 U/week, increased to 60,000 U/week if response was inadequate) and 141 patients to darbepoetin α (3.0, 5.0 and 9.0 $\mu\text{g}/\text{kg}$ every 2 weeks), hematopoietic response ranged from 66% (95% CI: 46,86) to 84% (95% CI: 67,100).⁶² Hematopoietic response rates for the 3.0 $\mu\text{g}/\text{kg}$ and 5.0 $\mu\text{g}/\text{kg}$ cohorts were 66% and 84%, respectively, compared with 63% for rHuEPO.⁶³ Generally, not only did higher doses of darbepoetin α result in higher hematopoietic response rates, but they were also associated with faster times to response, greater change from baseline Hb, and greater decreases in RBC transfusions during treatment. Overall, darbepoetin α was demonstrated to be effective at doses above 1.5 $\mu\text{g}/\text{kg}/\text{week}$ and 3.0 $\mu\text{g}/\text{kg}$ every 2 weeks, and no loss of dose efficiency was noted when the dosing interval was extended from once weekly to once every 2 weeks.⁶⁴ There also appeared to be a dose-response relationship in the proportion of patients achieving a Hb response and correction (Hb increase to ≥ 12 g/dL), and the mean change in Hb from baseline in a placebo-controlled study of 66 patients with lymphoproliferative malignancies who were receiving multicycle chemotherapy.⁶⁵ Furthermore, when the results of two trials were compared, it was noted that the dose-response of darbepoetin α appeared to be

similar in patients with lymphoproliferative and solid tumors.⁶⁶

A phase III, placebo-controlled trial that evaluated data from 314 patients indicated that once-weekly darbepoetin α was well tolerated and effective in reducing transfusion requirements and raising Hb.⁶⁷ The activity of darbepoetin α has also been demonstrated in patients who were not receiving chemotherapy, with hematopoietic response rates (Hb ≥ 12 g/dL or ≥ 2 g/dL increase in Hb from baseline) of 100% observed at the highest once-weekly dose.⁶⁸ Results from a phase II clinical trial indicate that darbepoetin α can improve hematopoietic response rates when given as infrequently as once every 3 weeks, and a dose-response relationship was observed at this dosing interval.⁶⁹

The dose-response relationship for darbepoetin α when administered in three different *loading phase/maintenance phase* schedules has also been explored, and results suggest that early, higher doses of darbepoetin α (lasting either 4 weeks or until Hb has increased to ≥ 12 g/dL), followed by lower and/or less frequent doses may provide an optimal erythropoietic response.⁷⁰ In this study, rHuEPO (40,000 U/week, with a dose increase to 60,000 U/week if response was inadequate by week 8) was the active control. After 4 weeks of therapy the mean change in Hb was approximately 80% greater in the three darbepoetin α groups than in the rHuEPO group. Despite the reduction in dose in the darbepoetin α groups in the latter part of the study, the mean change in Hb from baseline to the end of the study was still approximately 30% greater following treatment with darbepoetin α than with rHuEPO.

Extended dosing intervals, such as those being explored in the darbepoetin α clinical trials, mean that particular attention should be paid to patients' compliance and to the difficulty in implementing dose reductions in a timely fashion if needed. The results from these studies indicate that, with darbepoetin α at least, the majority of patients may be able to respond to therapy, suggesting that titration rather than removal of therapy may be appropriate.

Conclusions

Extensive studies have demonstrated the clinical efficacy of rHuEPO in improving Hb levels, transfusion rates and QOL in patients with chronic cancer-associated anemia. While further research is needed to refine our understanding of factors that are predictive of response to rHuEPO, a number of

tools are currently available. Assessment of baseline serum endogenous EPO levels should be obtained before a chemotherapy cycle in patients with lymphoma or myeloma (but not in solid tumors), so that only patients with a relatively impaired EPO response to anemia are given rHuEPO. Two weeks after starting rHuEPO therapy, measurement of early indicators of erythropoietic marrow response (such as change in Hb >0.3 – 0.5 g/dL or in sTfR >20 – 25% over baseline) can be recommended. As an inadequate iron supply is likely to limit the erythropoietic response to rHuEPO, patients should be assessed at baseline as well as during therapy for the presence of absolute or relative iron deficiency. Serum ferritin values below 40–100 $\mu\text{g/L}$ identify absence of iron stores, while measurement of transferrin saturation ($< 20\%$) or fraction of hypochromic RBCs ($> 10\%$) is the best way to diagnose functional iron deficiency. If a patient is severely iron deficient, it may be prudent to delay rHuEPO therapy until iron stores are replenished, or to treat the iron deficiency aggressively early in the course of rHuEPO therapy.

Although a number of factors may limit the efficacy of rHuEPO therapy, the application of reliable methods of predicting treatment response, the use of iron supplements and the development of new molecules promise significant improvements for patients suffering from chronic anemia comorbid with cancer. Prospective studies are warranted to confirm the value of treatment algorithms using rHuEPO or newer agents such as darbepoetin α .

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Mario Cazzola, Editor-in-Chief (Pavia, Italy)