

**PREDICTION OF RESPONSE TO OPTIMIZE OUTCOME OF TREATMENT WITH
ERYTHROPOIETIN**

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Abstract

Recombinant human erythropoietin (rHuEpo) has been shown to be effective in improving anemia in a proportion of cancer patients. The response rate is around 60 % but varies considerably according to baseline hematocrit and transfusion needs, as well as the response criteria used. Response is not greatly influenced by the type of tumor, except in situations of major marrow involvement and limited residual hematopoiesis, or in the presence of specific mechanisms of anemia, such as hemolysis, splenomegaly, bleeding, hemodilution, or ineffective erythropoiesis. Stem cell damage by previous therapy as well as marrow suppression by current intensive chemotherapy can impair response. Besides its intensity, the type of chemotherapy may not be critical, although patients undergoing platinum-based chemotherapy may respond faster than those receiving non-platinum regimens. Complications such as infections, bleeding or nutritional deficiencies may have a major negative impact on outcome. An important response-limiting factor is functional iron deficiency, i.e. an imbalance between iron needs in the erythropoietic marrow and iron supply, which depends on the level of iron stores and its rate of mobilization. Functional iron deficiency is best monitored by the percentage of hypochromic red cells, and oral or intravenous iron supplements should be given when this percentage rises above 10 %. All these factors explain why the response rate is only about 60 %. Therefore, it would be interesting to develop models that could help predict response to rHuEpo, in order to select the most appropriate cancer patients for this therapy. Few baseline parameters have been shown to be highly predictive of response in patients with solid tumors, although most studies in patients with myeloma or lymphoma have indicated that patients with a low baseline serum Epo level will respond better. Early changes after 2 to 4 weeks of treatment are also of great interest. Among these early changes, increments of serum transferrin receptor (sTfR), reticulocytes and hemoglobin, as well as the persistence of elevated ferritin or Epo levels, have all shown some predictive value. Combination of baseline serum Epo and the 2-week increment of sTfR or hemoglobin may provide the best prediction of response.

Introduction

Many patients with neoplastic disease develop anemia, irrespective of whether they are suffering from solid tumors or hematological malignancies ¹⁻³. Clinical studies have shown that recombinant human erythropoietin (rHuEpo) therapy can ameliorate the anemia associated with cancer and chemotherapy, reduce the need for transfusions and possibly improve the quality of life ⁴. A decrease in transfusion requirements is the major objective of rHuEpo therapy, reducing the cost, inconvenience, and potential adverse effects of blood transfusions. However, large doses are generally required and many patients do not respond even to very high doses of rHuEpo. It is therefore important to be able to recognize and possibly correct conditions adversely affecting response to rHuEpo. When no such particular condition can be identified, it would also be of great interest to have at one's disposal predictive algorithms of response, so that patients very likely to respond can be selected for therapy and prolonged ineffective use of an expensive medication can be avoided in those patients with a low probability of response.

Mechanisms of the anemia of cancer

The pathogenesis of the anemia of cancer is multifactorial ¹⁻³. A number of causes are frequently present and it is therefore difficult to identify a single causative factor in individual patients. Red cell loss may result from hypersplenism, blood losses consecutive to hemorrhage or iatrogenic phlebotomy, and autoimmune or microangiopathic hemolysis. Red cell production may be diminished by bone marrow infiltration, marrow necrosis, hemophagocytosis, myelofibrosis, deficiency of erythropoietic cofactors (folic acid, vitamin B12, iron), or infections. These mechanisms of anemia are much more prevalent in hematologic malignancies, but it is always important to identify them because specific therapeutic intervention can often be effective.

However, the so-called « anemia of chronic disorders » (ACD) has been found to play a major role in the pathogenesis of cancer-associated anemia. ACD is characterized by inadequate production of erythropoietin, inhibition of the proliferation of erythroid progenitor cells in the bone marrow and disturbances of iron utilization⁵. In cancer patients, a number of immunomodulatory peptides (cytokines), such as interleukin-1 and tumor necrosis factor, are produced and released by macrophages and other cells and appear to be involved in the pathogenesis of ACD⁶.

Anemia in cancer patients can also be caused or aggravated by therapy with antineoplastic agents. In particular, treatment with platinum, but not with other chemotherapeutic agents, has been associated with impairment of erythropoietin production⁷.

Design of therapy

The rate of response to rHuEpo in patients with cancer vary widely among published studies. This is due in part to differences in disease- and treatment- related factors, but this also reflects large differences in dose, frequency and route of administration, duration of therapy and the response criteria used. There is a clear dose-response effect with rHuEpo and most studies in cancer patients have used doses in the range of 300-900 U/kg/wk, well above those given to renal failure patients. The more convenient subcutaneous route of administration has been shown to ensure more favorable pharmacokinetics⁸ that translates into higher efficacy⁹ in renal failure patients. Most trials administered rHuEpo thrice weekly, a schedule demonstrated to be more efficient than daily injections in normal subjects¹⁰, but it remains to be shown whether weekly injections are as effective. The duration of treatment is of critical importance. Whereas there was no significant difference in the rate of transfusions between placebo and rHuEpo-treated patients during the first month of therapy, the difference became highly significant during the second and third months of treatment⁴. This is due to the fact that expansion of the erythropoietic marrow in response to rHuEpo is very gradual

and achieves maximum activity only after several weeks of treatment ¹¹. The response rate can thus be further improved when patients are treated for 6 months or more ¹².

The criteria used for defining response are determinant in the final evaluation of efficacy. It is obvious that trials employing less stringent response criteria will report better outcome. The patient's hematologic parameters at baseline are also of importance. Patients with more severe anemia and more needs for transfusion probably have a lower probability of achieving a target hematocrit. Pretreatment hematocrit was an important factor when rHuEpo was given for the prevention of anemia ¹³ but no longer when it was given after anemia was well established ¹⁴. This has been very well illustrated in animal studies in which rHuEpo was much more "efficient" when it was started before the administration of 5-FU because it could then increase the hematocrit better while myelosuppression was not yet occurring ¹⁵. Uniform response criteria can thus be proposed for transfused and untransfused, severely or not severely anemic cancer patients (table 1). Complete response is defined by normalization of the hematocrit, major response by the abolition of transfusion needs *and* an hematocrit increment greater than 6 percentage points *and* achievement of an hematocrit higher than 30 %, while minor response corresponds to only one of the two last criteria or a reduction of transfusion requirements by at least 50 %. When rHuEpo is given to prevent anemia during chemotherapy, complete response can be defined by maintenance of a normal hematocrit, major response by a drop of the hematocrit by less than 6 percentage points, and minor response by a larger drop in hematocrit but without need for transfusion.

Factors influencing response

It is thus clear that a number of disease- and treatment- related factors may influence response to rHuEpo. Except when there is major invasion by cancer cells and limited residual normal hematopoiesis, marrow involvement by the tumor does not appear to limit the efficacy of rHuEpo ^{4,16}. The type of tumor has generally not influenced the response rate, provided that no other specific mechanism of anemia is at work.

Patients with multiple myeloma or low grade lymphoma apparently have similar response rates^{17,18}. Although there were no apparent differences between hematologic and non-hematologic malignancies in the largest study published⁴, there has been a suggestion that patients with breast or colon cancer¹⁹ but not those with squamous cell carcinoma²⁰ may respond less well than patients with myeloma.

Stem cell damage by previous chemotherapy should considerably interfere with response to rHuEpo, but curiously this has not been studied so far. However, the poorer response obtained in patients with lower platelet counts may in fact just indicate that^{17,18}. For patients treated concomitantly with chemotherapy, there is no marked difference between those receiving platinum-based regimens^{21,22} and those receiving other forms of chemotherapy^{17,18,23}. In the largest study published⁴, patients receiving platinum-based chemotherapy responded more rapidly than those receiving other combinations but the overall response rate was similar in the 2 groups. However, dose intensity of the two forms of chemotherapy was not assessed and it is therefore impossible to compare the degrees of myelosuppression induced by chemotherapy and thus the capacity of rHuEpo to overcome it. Patients receiving chemotherapy of moderate intensity respond as well as those not receiving concomitant chemotherapy⁴. It is however probable that more intensive chemotherapy regimens would be associated with lower response rates.

Complications of chemotherapy, such as inflammation, infections, nutritional deficiencies or bleeding, may have a negative impact upon response²⁴. Functional iron deficiency is a major factor limiting the efficacy of rHuEpo therapy. It is defined as an imbalance between iron needs in the erythroid marrow and iron supply which depends on the level of iron stores and its rate of mobilization. This may occur even in the presence of large iron stores when storage iron release is impaired, as it is the case in the anemia of chronic disorders²⁵. Functional iron deficiency is best diagnosed by a percentage of hypochromic red cells greater than 10 %²⁶, a parameter calculated by some automated hematologic cell counters. Alternatively, it can also be suspected when transferrin saturation falls below 15 %. Because there is some concern that tumor cells may need iron for optimal growth²⁷, routine iron supplementation of all cancer patients receiving rHuEpo is not recommended, except when absolute iron deficiency is present, i.e. when serum ferritin is below 12

$\mu\text{g/L}$. Otherwise, iron supplements can be given when the percentage of hypochromic red cells is greater than 10 % and discontinued as soon as it returns to normal values.

Predictive models

As the response rate appears to vary considerably among patients treated similarly, it would be interesting to identify possible prognostic factors of response. Because clinical efficacy cannot be assessed before weeks of treatment, identification of early predictors of response could help provide the benefits of rHuEpo therapy to as many anemic cancer patients as possible while avoiding prolonged ineffective use of an expensive medication.

This has first been proposed in patients with the anemia of renal failure²⁸. The best prediction by baseline parameters only was obtained with pretreatment soluble transferrin receptor (sTfR) and fibrinogen : there was a 100 % response rate when both were low, versus only 29 % when there were both high, and 67 % when one was low and the other high. Changes of sTfR after 2 weeks of treatment were also predictive (table 2). When the 2-week sTfR increment was $\geq 20\%$, the response rate was 96 %. When sTfR increment was $< 20\%$, the response rate was 100 % when baseline sTfR was low and fibrinogen normal, 12 % when baseline fibrinogen was elevated and 62 % when baseline fibrinogen was normal but baseline sTfR high. These prognostic factors illustrate the importance of the early erythropoietic response (changes of sTfR levels), subclinical inflammation (fibrinogen) and functional iron deficiency (baseline sTfR).

In cancer patients, much attention has been paid to the possible value of baseline serum Epo because it was thought that patients would respond better if they had a defect in their capacity to produce Epo as compared to those whose anemia was accompanied by adequate serum Epo levels. Studies in patients with solid tumors have failed to confirm any predictive value of baseline Epo even when Epo deficiency was demonstrated in all or part of the patients^{4,22,29,30}. As Epo levels must be interpreted in relation to the degree

of anemia, the ratio of observed to predicted Epo levels (O/P ratio) represents a better assessment of the adequacy of Epo production ³¹. In patients with hematologic malignancies, it has been observed that low baseline serum Epo levels ¹⁴ or decreased O/P ratio ²³ were associated with a significantly lower probability of response. This has been confirmed in large multicenter trials in patients with multiple myeloma or non-Hodgkin's lymphoma ^{17,18}. An O/P ratio < 0.9 was found to be associated with high response rates, whereas patients with an O/P ratio > 0.9 rarely benefited from therapy ³².

As many in vitro and animal studies have demonstrated that several cytokines, including IL-1, TNF- α , and IFN- γ , strongly inhibited normal erythropoiesis and that this effect can be overcome only with large doses of rHuEpo, Ludwig ¹⁴ examined the possible predictive values of serum levels of these cytokines, but the results were disappointing. This is not entirely surprising since serum levels of these cytokines may not be relevant, whereas local intramedullary levels may be much more important but non-evaluatable.

As compared to baseline parameters, early changes observed after 2 weeks of treatment could be more informative. A rapid elevation of hemoglobin levels often predicted a good probability of later response ^{14,18,33}. An increase of reticulocyte counts by $\geq 40,000/\mu\text{l}$ from baseline to week 2 or 4 appeared to be predictive of response but its discriminative power was weak ³³. In several studies, hematologic response to rHuEpo was strongly associated with early increases of sTfR levels after 1-2 weeks of treatment ^{23,30,32}. Ludwig ¹⁴ conducted the most thorough analysis and found that increases of hemoglobin, sTfR and reticulocytes, as well as decreases of serum Epo, ferritin, iron, C-reactive protein or neopterin after 2 weeks were all correlated with response.

Various models have sought to combine the predictive power of several parameters. In a study including equal numbers of patients with solid tumors or hematologic malignancies ¹⁴, if after 2 weeks of therapy Epo was $> 100 \text{ mU/ml}$ and hemoglobin had not increased by at least 0.5 g/dL , there was a 94 % probability of unresponsiveness; otherwise response was likely in 80 % of the patients (table 3). If serum Epo was $< 100 \text{ mU/ml}$ and hemoglobin concentration had increased by $\geq 0.5 \text{ g/dL}$, the probability of responses was 100 %; otherwise the probability of failure was 62 %. However, 34/80 patients did not fall

into any of these two categories and thus prediction was valid only in a little more than half of them. The predictive value of a decrease in serum Epo levels may have two explanations. Endogenous serum Epo could decrease as the hematocrit rose in responders, but the magnitude of the hematocrit changes by 2 weeks seemed to be too small. Erythropoietin appeared to accumulate in non-responders but it cannot be excluded that these patients were receiving more intensive chemotherapy than others and thus be more likely to have inappropriate increases of endogenous serum Epo values ³⁴. On the other hand, Epo could be utilized by the stimulated marrow, but this has been contradicted by many experimental data ^{35,36}. Alternatively, a serum ferritin value ≥ 400 ng/ml after 2 weeks predicted for failure in 88 % of the cases, whereas serum ferritin levels < 400 ng/ml predicted for success in 72 % of the cases. However, the specific cutpoint of 400 ng/ml cannot be extrapolated to other patients because it depends so much on the previous transfusion history.

In a subset of patients from a large multicenter study ⁴, some prediction of response could be derived from changes observed in reticulocytes and hemoglobin from baseline to week 2 of therapy ³³. Among patients not receiving chemotherapy (table 4), the response rate was poor when the 2-week increment of hemoglobin level was < 0.5 g/dL, but it was excellent when the hemoglobin level or reticulocyte count increased by ≥ 0.5 g/dL or $\geq 40,000/\mu\text{L}$, respectively. The predictive power of these parameters was much less substantial when the hemoglobin increased by ≥ 0.5 g/dL but the reticulocyte elevation was smaller. Adequate prediction of response could not be provided on the basis of hemoglobin and reticulocyte changes in patients receiving concomitant chemotherapy (table 5). Although some improvement in forecast could be obtained in patients increasing their hemoglobin by ≥ 1 g/dL after 4 weeks of treatment, predicting response on the basis of the response itself may appear to be trivial.

A combination of baseline parameters and early changes observed after 2 weeks of rHuEpo may provide another useful approach. Among evaluable patients treated in a large multicenter study ¹⁸, the failure rate was almost 90 % when baseline serum O/P Epo was higher than 0.9 or when serum O/P Epo was less than 0.9 but the hemoglobin increment by week 2 was < 0.3 g/dL (table 6). On the other hand, the success rate was around 90 % when baseline serum O/P Epo was less than 0.9 and hemoglobin increased by ≥ 0.3 g/d. In another large single center study ³², the combined use of baseline serum Epo and the 2-week

increment of sTfR proved to be very powerful (table 7). Only 18 % of patients with a baseline serum Epo greater than 100 mU/ml responded to treatment, and only 29 % responded when the baseline serum Epo was < 100 mU/mL but the 2-week sTfR increment was less than 25 %. On the other hand, the response rate was 96 % among patients with a low baseline serum Epo and a substantial sTfR elevation.

Conclusion

In conclusion, a number of simple algorithms have been proposed to help predict outcome of treatment with rHuEpo. These algorithms were generally based on a combination of the adequacy of baseline endogenous Epo production and early direct (changes in hemoglobin, reticulocytes or sTfR) or indirect (changes in serum Epo or ferritin) indicators of erythropoietic marrow response. These models should help ensure a better use of rHuEpo by providing it to as many anemic cancer patients as possible but only to those with an excellent chance of success. Some models underscore sensitivity and this permits to treat all potential responders. Other models give emphasis to specificity so that most failures can be predicted and rHuEpo therapy can be avoided or stopped early. Several of them achieve an overall accuracy of about 90 %. The respective value of these various algorithms remains to be confronted in a prospective study. However, the occurrence of complications such as infections or functional iron deficiency cannot be predicted as well and one should always monitor patients for their occurrence even when the probability of response was predicted to be high.

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Table 1. Criteria for response to rHuEpo

- *Complete response*
 - Normalize Hct value
- *Major response : all criteria*
 - Disappearance of transfusion needs
 - Hct increment $\geq 6\%$
 - Achieve Hct $\geq 30\%$
- *Minor response : any criteria*
 - Decrease of transfusion needs by at least 50 %
 - Hct increment $\geq 6\%$ but Hct $< 30\%$
 - Achieve Hct $\geq 30\%$ but Hct increment $< 6\%$

Table 2. Prediction of response in patients with renal failure treated with rHuEpo. Study by Beguin et al.²⁸.

2-wk sTfR increment	Parameter		Response (%)		
	Baseline fibrinogen	Baseline sTfR	Early	Late	Overall
≥ 20 %	-	-	73	23	96
< 20 %	Normal	< 3,500 µg/L	100	0	100
< 20 %	Normal	≥ 3,500 µg/L	38	24	62
< 20 %	High	-	0	12	12

Response = achievement of hematocrit ≥ 30 %. Overall response rate = 77 %.

sTfR = soluble transferrin receptor.

Table 3. Prediction of response in patients with the anemia of cancer treated with rHuEpo. Study by Ludwig et al.¹⁴.

Parameter at week 2		Patients	Response (%)	
Serum Epo (mU/mL)	Hb increment (g/dL)	N	Yes	No
< 100	≥ 0.5	15	100	0
≥ 100	< 0.5	31	6	94
< 100	< 0.5	30	70	30
≥ 100	≥ 0.5			

Response = Hb increment ≥ 2 g/dL. Overall response rate = 50 %.

Epo = erythropoietin; Hb = hemoglobin.

Table 4. Prediction of response in patients with the anemia of cancer not receiving chemotherapy and treated with rHuEpo. Study by Henry et al.³³.

Parameter at week 2		Patients	Response (%)	
Hb increment (g/dL)	Retic increment (/μL)	N	Yes	No
≥ 0.5	$\geq 40,000$	11	91	9
≥ 0.5	$< 40,000$	14	36	64
< 0.5	$\geq 40,000$	6	17	83
< 0.5	$< 40,000$	23	4	96

Response = hematocrit increment $\geq 6\%$. Overall response rate = 31 %.

Hb = hemoglobin; retic = reticulocyte.

Table 5. Prediction of response in patients with the anemia of cancer receiving chemotherapy and treated with rHuEpo. Study by Henry et al.³³.

Parameter at week 2		Patients	Response (%)	
Hb increment (g/dL)	Retic increment (/μL)	N	Yes	No
≥ 0.5	$\geq 40,000$	21	67	33
≥ 0.5	$< 40,000$	29	66	34
< 0.5	$\geq 40,000$	20	50	50
< 0.5	$< 40,000$	62	48	52

Response = hematocrit increment $\geq 6\%$. Overall response rate = 55 %.

Hb = hemoglobin; retic = reticulocyte.

Table 6. Prediction of response in patients with the anemia associated with multiple myeloma or non-Hodgkin's lymphoma and treated with rHuEpo. Study by Cazzola et al. {{18248}}.

Baseline O/P Epo	2-week Hb increment (g/dL)	Patients N	Response (%)	
			Yes	No
≥ 0.9	-	8	13	87
< 0.9	< 0.3	6	0	100
< 0.9	≥ 0.3	34	88	12

Response = Hb increment \geq 2 g/dL. Overall response rate = 65 %.

O/P Epo = ratio of observed-to-predicted serum erythropoietin; Hb = hemoglobin.

Table 7. Prediction of response in patients with the anemia of cancer treated with rHuEpo. Study by Cazzola et al. {{18252}}.

Baseline serum Epo (mU/ml)	2-week sTfR increment (%)	Patients N	Response (%)	
			Yes	No
≥ 100	-	17	18	82
< 100	< 25	7	29	71
< 100	≥ 25	24	96	4

Response = hemoglobin increment ≥ 2 g/dL. Overall response rate = 58 %.

Epo = erythropoietin; sTfR = soluble transferrin receptor.