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Chapter XV

Predictive factors for response of anemia to recombinant human erythropoietin

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Introduction

Patients with solid tumors or hematological malignancies often develop anemia at diagnosis or in the course of the disease (Means et al. 1992; Beguin 1996; Moliterno et al. 1996; Groopman et al. 1999). Many studies have shown that recombinant human erythropoietin (rHEpo) therapy can ameliorate the anemia associated with cancer and chemotherapy, reduce the need for transfusions and improve quality of life as well as work capacity. However, as many as 30–50% of the patients do not respond, even to very high doses of rHEpo. It is, therefore, important to be able to recognize and correct conditions adversely affecting response to rHEpo, in particular functional iron deficiency. 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. Thereby patients can be selected on the basis of their probability to achieve a good response to treatment and prolonged ineffective use of an expensive medication can be avoided in those patients with a low probability of response. In this paper, we will review factors potentially affecting response to rHEpo and comment on the use of predictive algorithms.

Factors influencing response to rHuEpo

Criteria of response

Before analyzing factors potentially affecting response to rHEpo, it is critical to define response criteria. Various trials in miscellaneous indications have employed very different response criteria. Trials employing less stringent criteria for defining response are very likely to report better outcome.

Therefore, uniform response criteria should be proposed for transfused and untransfused, severely or not severely anemic cancer patients. However, these criteria should necessarily be partly different when rHEpo is used for the prevention or the treatment of anemia (Table 1). Prevention means that rHEpo is used in a nonanemic patient to avert the occurrence of anemia after chemotherapy or other interventions. Treatment signifies that rHEpo is given to reverse an anemia present at diagnosis or developing in the course of the disease. Complete response should be defined by the absence of anemia, i.e. maintenance (prevention) or achievement (treatment) of a normal hematocrit. When treating an anemia, a major response delineates the achievement of a significant improvement approaching a normal situation, whereas a minor response corresponds to a measurable though less dramatic effect: a major response can be defined by the abolition of transfusion needs *and* a hematocrit increment greater than 6 percentage points *and*

Table 1. Criteria of response to rHEpo

Treatment of anemia
- Complete response
  - Normalize Hct/Hb value
- Major response: *all criteria should be fulfilled*
  - No transfusion requirement
  - Hct increment ≥ 6% (Hb increment ≥ 2 g/dl)
  - Achieve Hct ≥ 30% (Hb ≥ 10 g/dl)
- Minor response: *one criterion*
  - Decrease of transfusion needs ≥ 50%
  - Hct increment ≥ 6% but Hct < 30% (Hb increment ≥ 2 g/dl but Hb < 10 g/dl)
  - Achieve Hct ≥ 30% but Hct increment < 6% (Hb ≥ 10 g/dl but Hb increment < 2 g/dl)
- Failure: *one criterion*
  - Decrease of transfusion needs < 50%
  - Hct increment < 6% and Hct < 30% (Hb increment < 2 g/dl and Hb < 10 g/dl)

Prevention of anemia
- Complete response
  - Maintain normal Hct/Hb value
- Major response: *all criteria should be fulfilled*
  - No transfusion requirement
  - Hct decrement < 6% (Hb decrement < 2 g/dl)
- Minor response: *all criteria should be fulfilled*
  - No transfusion requirement [Hb ≥ 8 g/dl]
  - Hct decrement ≥ 6% (Hb decrement ≥ 2 g/dl)
- Failure:
  - Transfusion [Hb < 8 g/dl]

achievement of a hematocrit higher than 30%; a minor response corresponds to only one of the two last criteria or a reduction of transfusion requirements by at least 50%. When rHEpo is given to prevent anemia, a major response corresponds to a drop of the hematocrit by less than 6 percentage points and a minor response to a larger drop in hematocrit but without need for transfusion (Hb > 8 g/dl).

Treatment schedules

Varying rates of response to rHEpo among studies also reflect differences in dose, frequency and route of administration, duration of therapy and the form of erythropoietin used (Table 2).

There is a clear dose-response effect with rHEpo 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. For instance, treatment of anemia in patients with advanced gastrointestinal cancer was much more successful with 10000 U compared with 2000 U t.i.w. (Glimelius et al. 1998). Similarly, daily doses of 5000 U were more effective than lower doses and 10000 U did not bring about further improvement in anemic patients with myeloma or lymphoma (Cazzola et al. 1995). The more convenient subcutaneous route of administration has been shown to ensure more favorable pharmacokinetics (Macdougall et al. 1989) that translates into higher efficacy in renal failure patients (Paganini et al. 1995). Most trials administered rHEpo thrice weekly, a schedule demonstrated to be more efficient than daily injections in normal subjects (Breymann et al. 1996). In normal volunteers treated for one month, weekly injections have been shown to produce erythropoietic responses similar to those achieved with t.i.w. schedules (Cheung et al. 2000). Although once-weekly dosing has been shown to increase Hb, decrease transfusions and improve quality of life in a fashion analogous to what is obtained with thrice-weekly administration (Gabrilove et al. 2000), the equivalence of the two schedules remains to be proven in prospective trials.

Whereas there is no known difference in the efficacy and safety profile of Epoetin-α (Janssen-Cilag), Epoetin-β (Roche) or gene-activated Epoetin (Aventis), novel long-acting erythropoietin molecules may also considerably prolong exposure to the active drug and thus improve the efficacy of therapy with fewer injections. One of these molecules, named novel-erythropoiesis stimulating protein (NESP) or darbepoietin alfa (Amgen), has already been tested in prospective clinical trials in renal failure or cancer patients (Macdougall 2000).

The duration of treatment is of critical importance. In the largest trial published so far, whereas there was no significant difference in the rate of transfusions between placebo and rHEpo-treated patients during the first month of therapy, the difference became highly significant during the second

Table 2. Factors potentially limiting response to rHEpo

Factor	Factor influences response significantly		Comments
	Yes	No	
Factors relating to rHEpo treatment			
• Dose	×		At least 150 U/kg t.i.w.
• Route	×		SC > IV
• Frequency		×?	Weekly ≈ t.i.w. ?
• Duration	×		Needs at least 2–3 months
• Type of rHEpo		×	Long-acting Epo: less frequent dosing
Factors relating to the patient			
• Age		×	
• Sex		×	
Factors relating to the disease			
• Type of cancer		×	
• Marrow infiltration		×	Unless massive (acute leukemia)
• Mechanisms of anemia			
Hemolysis	×		
Bleeding	×		
Hypersplenism	×		
Marrow necrosis or fibrosis	×		
Hemophagocytosis	×		
Folate, B12, iron deficiency	×		
Factors relating to chemotherapy			
• Type of chemotherapy			
Platinum vs non-platinum		×	
Intensity of chemotherapy	×		Not effective if intensified chemotherapy
• Previous stem cell damage	×		Low platelet count
• Complications			
Infection	×		
Inflammation	×		
Bleeding	×		
• Surgery	×		Bleeding + impaired iron release
Functional iron deficiency			*A major cause of treatment failure*
• Caused by ACD	×		
• Induced by rHEpo therapy	×		

and third months of treatment (Abels 1992). In that trial also, the efficacy of rHEpo appeared to be lower in cancer patients not treated with chemotherapy because erythropoietin was given for a shorter duration (and at a lower dose). This is due to the fact that expansion of the erythropoietic marrow in response to rHEpo is very gradual and achieves maximum activity only after several weeks of treatment (Beguin et al. 1995). The response rate can thus be further improved when patients are treated for 6 months or more (Henry et al. 1994). In order to maximize "time with response", it would be desirable to achieve a faster response. Whether this can be achieved without total cost increase by providing higher doses of rHEpo for a short period of time (e.g. one month) followed by lower maintenance doses remains to be demonstrated.

Disease-associated factors

A number of mechanisms can be involved in the pathogenesis of anemia associated with cancer (Means et al. 1992; Beguin 1996; Moliterno et al. 1996) and, therefore, interfere with response to rHEpo in individual patients (Table 2). 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 be effective. However, cancer-associated anemia is often delineated by the more general features of the so-called "anemia of chronic disorders" (ACD). ACD is a cytokine-driven condition characterized by inadequate production of erythropoietin, inhibition of the proliferation of erythroid progenitor cells in the bone marrow and disturbances of iron utilization (Sears 1992; Means et al. 1992).

The patient's hematologic parameters at baseline may also be of importance. Patients with more severe anemia and more needs for transfusion presumably have a lower probability of achieving a target hematocrit. Pretreatment hematocrit was an important factor when rHEpo was given for the prevention of anemia (Crawford et al. 1994) but no longer when it was given after anemia was well-established (Ludwig et al. 1994). This has been very well illustrated in animal studies in which rHEpo 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 occurring yet (Matsumoto et al. 1990).

Other factors have been examined (Table 2). Age and sex have not been reported to influence response. 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 rHEpo (Abels 1992; Oster et al. 1990). 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 (Österborg et al. 1996; Cazzola et al. 1995). Although there were no apparent differences between hematologic and non-hematologic malignancies in the largest study published (Abels 1992), there has been a suggestion that patients with breast or colon cancer (Ludwig et al. 1993a), but not those with squamous cell carcinoma (Ludwig et al. 1993b), may respond less well than patients with myeloma. However, these discrepancies most likely relate to differences in chemotherapy duration and intensity among them.

Chemotherapy-related factors

Chemotherapy may also hamper response (Table 2). Anemia in cancer patients is often 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 production (Wood et al. 1995). Patients who have been heavily pretreated with chemotherapy usually experience severe stem cell damage that should considerably interfere with response to rHEpo. Indeed, the poorer response obtained in patients with lower platelet counts probably just indicates that (Österborg et al. 1996; Cazzola et al. 1995).

For patients treated concomitantly with chemotherapy, there is no marked difference between those receiving platinum-based regimens (Markman et al. 1993; Cascinu et al. 1994) and those receiving other forms of chemotherapy (Cazzola et al. 1992; Österborg et al. 1996; Cazzola et al. 1995). A multicenter study showed the same Hb response (speed and magnitude) in patients receiving platinum-based vs other forms of chemotherapy (Pawlicki et al. 1997). In the largest study published (Abels 1992), patients receiving platinum-based chemotherapy responded more rapidly than those receiving other combinations but the overall response rate was similar in the two 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 rHEpo to overcome it. Patients receiving chemotherapy of moderate intensity respond as well as those not receiving concomitant chemotherapy (Abels 1992). It is, however, probable that more intensive chemotherapy regimens would be associated with lower response rates. In particular, rHEpo therapy is not capable to stimulate erythropoiesis in the early period following intensified

chemotherapy with autologous bone marrow transplantation (Link et al. 1994).

On the other hand, surgery or complications of chemotherapy, such as inflammation, infections or bleeding, may have a major negative impact upon response (Table 2). Chronic or acute bleeding is a frequent complication of cancer, and this is particularly true in thrombocytopenic patients. Surgery is often followed by a transient loss of response to rHEpo, not only because it may be complicated by significant blood losses, but also because postoperative erythropoiesis is limited by the inflammatory effect of surgery on iron metabolism that impairs iron reutilization (Biesma et al. 1995). Any source of inflammation, be it related to surgery, trauma, infection or concomitant disorders will interfere with response to rHEpo. In particular, infections have been shown to cause hyporesponsiveness to rHEpo in patients with the anemia of renal failure (Danielson et al. 1995). Infections occur frequently in cancer patients receiving chemotherapy. This will slow or totally prevent response at the beginning of rHEpo therapy, as well as abrogate response when the target Hb is being maintained with lower doses, requiring higher doses to be started again.

Functional iron deficiency

Functional iron deficiency is a major factor limiting the efficacy of rHEpo therapy (Table 2). It is defined as an iron deficit in the functional erythroid compartment, the result of an imbalance between iron needs in the erythroid marrow and iron supply (Fig. 1). This may occur even in the presence of large iron stores, when storage iron release is inadequate. Iron requirements are determined by the overall level of erythropoietic activity and iron availability depends on the level of iron stores and their rate of mobilization. Functional iron deficiency can occur before rHEpo is started, either because iron stores are absent (true iron deficiency) or because storage iron release is impaired, a typical feature of the anemia of chronic disorders (Fillet et al. 1989). It can also develop in the course of erythropoietin therapy when iron stores become progressively exhausted or, more frequently, when the increased iron needs of an expanding erythroid marrow cannot be matched by sufficient mobilization of often enlarged iron stores. Indeed, the vast majority of renal failure patients treated with rHEpo develop functional iron deficiency that limits seriously their erythropoietic response (Macdougall 1999). Although this has not been specifically examined in cancer patients treated with rHEpo, there is every reason to believe that its prevalence is very high in this setting as well.

Functional iron deficiency is best diagnosed by a percentage of reticulocytes with a hemoglobin content lower than 26 pg (Brugnara et al. 1994;

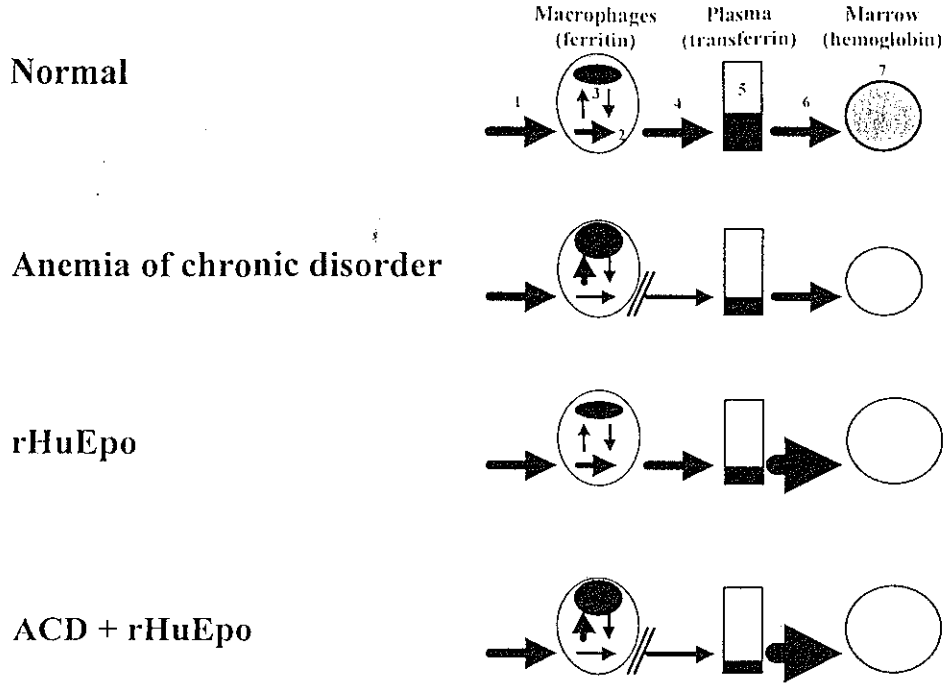


Fig. 1. Iron metabolism in various conditions illustrates functional iron deficiency
A. *Normal*: when senescent red cells are phagocytosed (1) by macrophages, iron is recycled into a transit pool (2); part is stored as ferritin (hatched area) (3) and the rest is released (4) to plasma transferrin (5); iron is then taken up (6) by the erythroid marrow (7) to produce normal red cells. Iron supply (4) by storage cells matches iron demand (6) by the erythroid marrow and transferrin remains adequately (20–40%) saturated (black filling) by iron (5).
B. *Anemia of chronic disorder (ACD)*: iron release by macrophages is blocked and more iron is stored as ferritin within these cells. Iron supply can no longer match iron demand by the erythroid marrow: transferrin saturation decreases (<20%), the erythroid marrow becomes functionally iron deficient and new red cells are hypochromic.
C. *Treatment with rHuEpo*: the erythroid marrow expands upon intense stimulation by erythropoietin. Its increased demand for iron cannot be matched by storage iron release: transferrin saturation decreases (<20%), the erythroid marrow becomes functionally iron deficient and new red cells are hypochromic.
D. *ACD treated with rHuEpo*: impaired iron supply and increased iron demand combine to decrease transferrin saturation and cause functional iron deficiency

Brugnara 1998) or a percentage of hypochromic red cells greater than 10% (Macdougall et al. 1992), both parameters calculated by some automated hematologic cell counters. Alternatively, it can also be suspected when transferrin saturation falls below 20%. On the other hand, serum ferritin is of very limited value, because it only gives an evaluation of iron stores without providing any hint on how these stores can be mobilized (Kooistra et al. 1991). Because there is some concern that tumor cells may need iron for optimal growth (Weinberg 1996), routine iron supplementation of all cancer patients receiving rHEpo is not recommended. The same is true for oral as well as intravenous iron supplementation. However, this should be balanced with the fact that transfusion of one red blood cell 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 below 40–100 µg/L, a level associated with absence of iron stores in the anemia of chronic disorders. Otherwise, iron supplements should be given when the transferrin saturation is below 20% or the percentage of hypochromic red cells 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 (Macdougall et al. 1996) but that intravenous iron both substantially improves response when rHEpo therapy is instituted (Macdougall et al. 1996) and allows considerable (in the order of 40%) reduction in rHEpo dose requirements during the maintenance phase (Fishbane et al. 1995; Besarab et al. 2000). The safety profile (Sunder-Plassmann et al. 1997) 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 due to free iron release) (Drueke et al. 1997). Iron usage has not been energetically pursued in clinical trials of rHEpo 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 really need iron together with erythropoietin because their iron stores (ferritin) are not decreased. In addition, iron has only been given orally, a method proved 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 the anemia of chronic disorders (Sears 1992; Means et al. 1992). The efficacy of intravenous iron after failure of oral iron to correct functional iron deficiency and improve anemia has been well documented in juvenile chronic arthritis, another form of anemia of chronic disorder (Martini et al. 1994). Although this has not been formally studied in the anemia of cancer, intravenous administration of 100 mg elemental iron every week or 200 mg every other week will ensure the best utilization of any given dose of rHEpo. Future clinical trials should investigate the use of intravenous iron in cancer patients treated with rHEpo to demonstrate greater efficacy and/or lower erythropoietin requirements.

Predictive models

Introduction

Because response rates vary considerably among patients treated similarly and clinical efficacy cannot be assessed before weeks of treatment, identification of early predictors of response would be of major interest. The use of such prognostic factors of response could help provide the benefits of rHEpo therapy to as many anemic cancer patients as possible, while avoiding prolonged ineffective use of an expensive medication.

A predictive algorithm of response to rHEpo has first been proposed in the setting of the anemia associated with renal failure (Fig. 2) (Beguin et al. 1993b). The best prediction by baseline parameters only was obtained with pretreatment soluble transferrin receptor (sTfR) and fibrinogen. Serum sTfR represents a quantitative measure of erythropoietic activity (Huebers et al. 1990) and is also increased when functional iron deficiency develops (Skikne et al. 1990). It can now be measured by several commercial immunoassays. There was a 100% response rate when both sTfR and fibrinogen were low, versus only 29% when they were both high, and 67% when one was low and the other high. Changes of sTfR after 2 weeks of treatment were also predictive. When the 2-week sTfR increment was ≥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

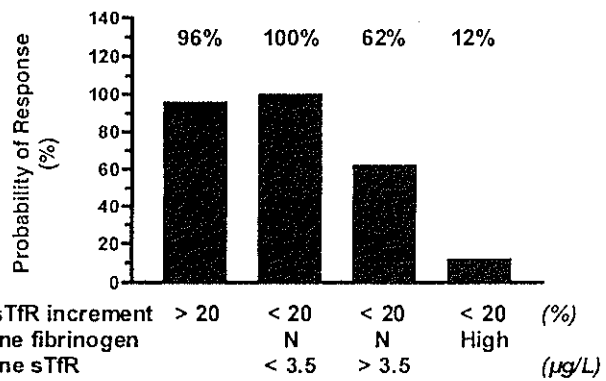


Fig. 2. Prediction of response to rHuEpo in the anemia of renal failure by baseline sTfR (an indicator of functional iron deficiency), baseline fibrinogen (a parameter of inflammation) and the 2-wk sTfR increment (a marker of increasing erythropoietic activity) (Beguin et al. 1993b)

erythropoietic response (changes of sTfR levels), subclinical inflammation (fibrinogen) and functional iron deficiency (baseline sTfR).

Baseline parameters

Theoretically, cancer patients with a defect in their capacity to produce Epo would be more likely to respond to rHEpo than those with adequate serum Epo levels for their degree of anemia. 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 (Beguin et al. 1993a). Based on regression equations obtained in reference subjects, predicted log (Epo) values can be derived for each Hct, and O/P ratios of observed-to-predicted values can be calculated (95% confidence limits 0.80–1.20) (Beguin et al. 1993a). In patients with hematologic malignancies, it has been observed that low baseline serum Epo levels (Ludwig et al. 1994) or decreased O/P ratio (Cazzola et al. 1992) were associated with a significantly higher probability of response. This has been confirmed in large multicenter trials in patients with multiple myeloma or non-Hodgkin's lymphoma (Österborg et al. 1996; Cazzola et al. 1995). 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 (Cazzola et al. 1996). However, studies in patients with solid tumors have failed to confirm such a consistent predictive value of baseline Epo even when Epo deficiency was demonstrated in all or part of the patients (Abels 1992; Cascinu et al. 1994; Platanias et al. 1991; Ponchio et al. 1992; Oberhoff et al. 1998), although a study aiming at preventing anemia in patients with ovarian carcinoma undergoing platinum-based chemotherapy showed a trend for lower transfusion needs in those with an O/P ratio < 0.8 (ten Bokkel Huinink et al. 1998). Of importance, in patients treated with chemotherapy, serum Epo should be evaluated just prior to chemotherapy for its interpretation to be valid (Fig. 3). Indeed, without any change in hematocrit, serum Epo may be inappropriately elevated in the two weeks after chemotherapy compared to pre-chemotherapy values, most probably because myelosuppression then decreases Epo utilization by target cells (Beguin et al. 1991; Cazzola et al. 1998). Therefore, it cannot be excluded that the failure to predict response in solid tumor patients may just be related to an inadequate timing of serum Epo sampling.

Other baseline parameters have been examined as possible predictors of response. Pretreatment hematocrit is of course an important factor when rHEpo is given for the prevention of anemia (Crawford et al. 1994) but is no longer helpful when it is given after anemia is well established (Ludwig et al. 1994). Other measurements of erythropoietic activity, such as the reticulocyte count or sTfR levels were not predictive of response (Ludwig et al.

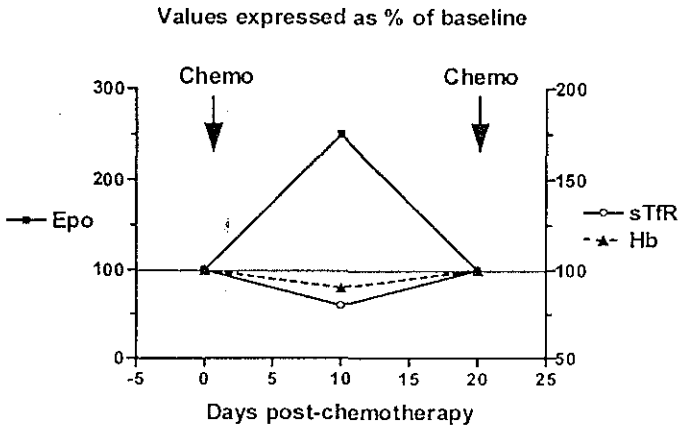


Fig. 3. Changes in serum Epo, Hb and sTfR after a chemotherapy cycle. Chemotherapy transiently causes an increase in serum Epo levels that is disproportionate to the degree of anemia

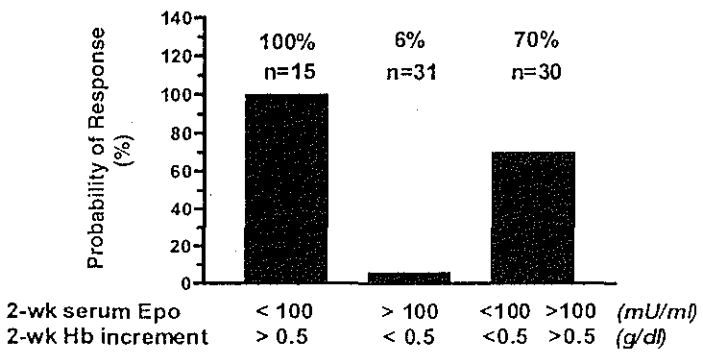


Fig. 4. Prediction of response to rHuEpo in the anemia of cancer by the week 2 absolute serum Epo level and the 2-wk Hb increment (Ludwig et al. 1994)

1994). Only large doses of rHuEpo can overcome the strong inhibition of erythropoiesis induced by such cytokines as IL-1, TNF-α and IFN-γ. Ludwig et al. (1994) 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 are very difficult to evaluate.

Early changes in erythropoietic parameters

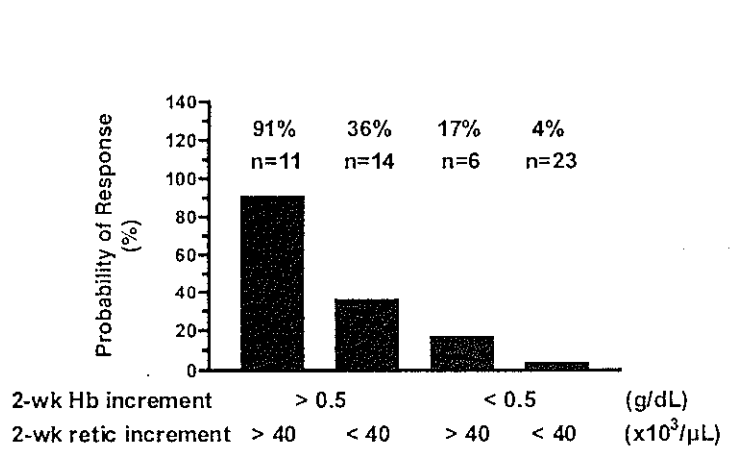
Early changes in parameters of erythropoietic activity observed after two weeks of treatment could be more informative. A rapid elevation of hemoglobin levels often predicted a good probability of later response (Ludwig et al. 1994; Henry et al. 1995; Cazzola et al. 1995). An increase of reticulocyte counts by ≥40000/μl from baseline to week 2 or 4 appeared to be predictive of response but its discriminative power was weak (Henry et al. 1995). In several studies, hematologic response to rHEpo was strongly associated with early increases of sTfR levels after 1–2 weeks of treatment (Ponchio et al. 1992; Cazzola et al. 1992, 1996). Ludwig et al. (1994) 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 two weeks were all correlated with response.

Predictive algorithms based on early changes

Various models have sought to combine the predictive power of several parameters. In a study including similar numbers of patients with solid tumors or hematologic malignancies (Ludwig et al. 1994), if after 2 weeks of therapy Epo was >100 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. If serum Epo was <100 mU/ml and hemoglobin concentration had increased by ≥0.5 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 for that. On the other hand, Epo could be utilized by an expanding erythroid marrow or conversely accumulate in non-responders, but it cannot be excluded that these later patients were receiving more intensive chemotherapy than others and thus be more likely to have inappropriate increases of endogenous serum Epo values (Beguin et al. 1991; Cazzola et al. 1998). 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 (Abels 1992), some prediction of response could be derived from changes observed in reticulo-

cytes and hemoglobin from baseline to week 2 of therapy (Fig. 5) (Henry et al. 1995). Among patients not receiving chemotherapy (Fig. 5A), 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 ≥40 000/μL, respectively. The predictive power of these parameters was much less substantial when the hemoglobin increased



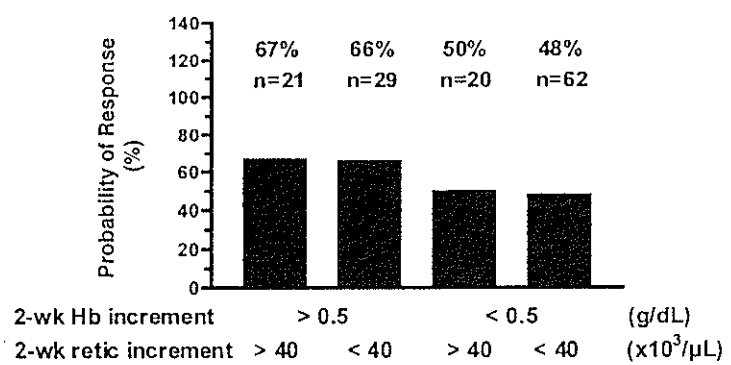


Fig. 5. Prediction of response to rHuEpo in the anemia of cancer by the 2-wk Hb and reticulocyte increments (Henry et al. 1995). A good prediction can be obtained in patients not receiving chemotherapy (A) but not in those receiving chemo-

by ≥0.5 g/dL but the reticulocyte elevation was smaller. Adequate prediction of response could not be provided on the basis of Hb and reticulocyte changes in patients receiving concomitant chemotherapy (Fig. 5B). 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.

Predictive algorithms based on a combination of baseline parameters and early changes

A combination of baseline parameters and early changes observed after 2 weeks of rHEpo may provide another useful approach. Among evaluable patients treated in a large multicenter study (Cazzola et al. 1995), 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 (Fig. 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. Similar findings were obtained in a smaller study in children with solid tumors: an O/P ratio <1.0 at baseline and a hemoglobin increment >0.5 g/dL after 2 weeks were associated with higher response rates (Leon et al. 1998). In another large single-center study (Cazzola et al. 1996), the combined use of baseline serum Epo and the 2-week increment of sTfR proved to be very powerful (Fig. 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.

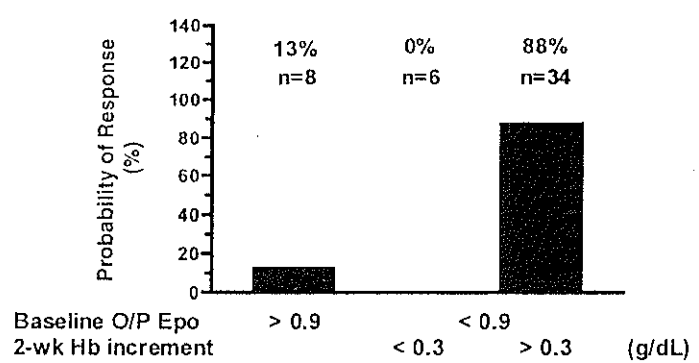


Fig. 6. Prediction of response to rHuEpo in the anemia associated with lymphoma or multiple myeloma by the baseline observed/predicted serum Epo ratio and the

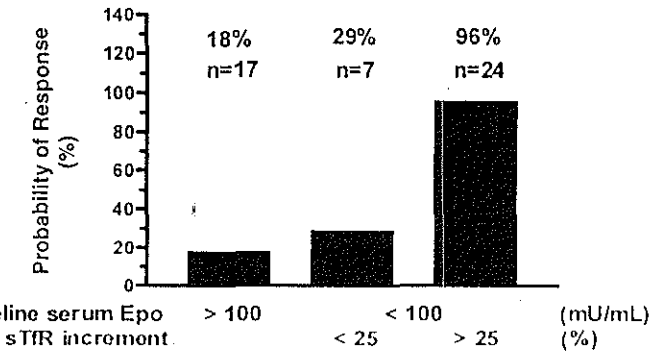


Fig. 7. Prediction of response to rHuEpo in the anemia of cancer by the baseline serum Epo level and the 2-wk sTfR increment (Cazzola et al. 1996)

Applicability of predictive factors

There are a number of theoretical reasons why some or all of these parameters might not be of value in certain situations (Table 3). While evaluation of endogenous Epo production may be relevant in various forms of anemia, it is of no interest in subjects in whom the aim of rHEpo therapy is to prevent an anemia that is not yet present, in those in whom better tumor oxygenation before radiotherapy or induction of fetal hemoglobin is sought, or in disorders characterized by universal Epo deficiency. Even among cancer patients, whereas low baseline serum Epo levels or decreased observed-to-predicted Epo levels (O/P ratio) were associated with a significantly higher probability of response in patients with hematologic malignancies (Ludwig et al. 1994; Österborg et al. 1996; Cazzola et al. 1995, 1996), this was usually not the case in patients with solid tumors (Abels 1992; Cascinu et al. 1994). On the other hand, hemoglobin increments after 2 weeks of treatment may be of value in steady state patients, but are of little help in transfused patients and in those in whom rHEpo is intended to prevent the occurrence of severe anemia but cannot avert some decrease in hemoglobin induced by phlebotomy or myelosuppressive treatments. Finally, changes in parameters directly reflecting erythropoietic activity, i.e. reticulocyte counts and sTfR, may be the most appropriate. However, changes in reticulocyte counts may simply reflect output of shift reticulocytes and not true expansion of erythropoiesis, and often have not been found to be a good indicator of response (Beguin et al. 1993b; Ludwig et al. 1994). Although sTfR levels represent the best quantitative measurement of total erythropoietic activity, they may also increase secondary to functional iron deficiency (Huebers et al. 1990). In addition, particularly in patients treated with chemotherapy, the timing of the evaluation of these parameters relative to chemotherapy may be critical for their interpretation. For instance, measuring serum Epo after chemotherapy may yield elevated levels compared to pre-chemotherapy values, without any change in hematocrit (Beguin et al. 1991).

Table 3. Theoretical value (yes = probably of value; no = probably of no value) of potential predictors of response to rHuEpo in various settings according to the indication for therapy (see text for discussion)

	Baseline Epo or O/P ratio	2-wk Hb increment	2-wk retic/sTfR increment
1. Prevention of anemia			
• Autologous blood donation	No	No	Yes
• Adjuvant treatment for phlebotomy	No	No	Yes
• Perisurgery	No	No (1)	No (1)
• Chemotherapy (planned)	Yes (2)	No	No
2. Correction of untransfused anemia			
• AIDS, inflammatory diseases, cancer, MDS, organ transplantation	Yes (2)	Yes	Yes
• Chemotherapy (ongoing)	Yes (2)	Yes (3)	Yes (3)
3. Reduction in transfusion requirements			
• AIDS, inflammatory diseases, cancer, MDS, organ transplantation	Yes (2)	No	Yes
• Chemotherapy (ongoing)	Yes (2)	No	Yes (3)
• Prematurity	No (4)	No	Yes
• Allogeneic stem cell transplantation	No (4)	No	No
4. Miscellaneous			
• Radiotherapy	No	Yes	Yes
• Orthostatic hypotension	No	Yes	Yes
• Induction of fetal Hb	No	No	No

Epo = erythropoietin; O/P Epo = ratio of observed-to-predicted Epo; Hb = hemoglobin; retic = reticulocytes; sTfR = soluble transferrin receptor.
(1) Treatment too short to be modified by changes in erythropoietic parameters.
(2) Epo deficiency in some forms of cancer (lymphoma, myeloma, some MDS) and chemotherapy (cisplatin).
(3) Timing of sample for measurement of predictor may be critical (see text).
(4) Not a real predictor because Epo deficiency is observed in virtually all patients.

Conclusion

Several algorithms have been proposed for patients with the anemia of cancer (Table 4). Their sensitivity (how well the algorithm identifies all those

Table 4. Comparison of various algorithms for prediction of response to rHuEpo (reproduced with permission from Beguin 1998)

Author	Ludwig et al. 1994	Henry et al. 1995	Henry et al. 1995	Cazzola et al. 1995	Cazzola et al. 1996
N patients	76	54	132	48	48
Disease	Cancer	Cancer (No chemotherapy)	Cancer (Chemotherapy)	Myeloma-NHL	Cancer
Overall response rate (%)	50	31	55	65	58
Prediction algorithm	Response if 2-week Epo < 100 mU/mL *and* Δ Hb ≥ 0.5 g/dL	Response if 2-week Δ retic ≥ 40000/μL *and* Δ Hb ≥ 0.5 g/dL	Response if 2-week Δ retic ≥ 40000/μL *and* Δ Hb ≥ 0.5 g/dL	Response if 2-week Δ Hb ≥ 0.3 g/dL *and* baseline O/P Epo < 0.9	Response if - 2-week Δ sTfR ≥ 25% *and* baseline Epo < 50 mU/mL
Sensitivity (%)	42*	59	19	97	88
Specificity (%)	100*	97	88	76	95
Positive predictive value (%)	100*	91	67	88	96
Negative predictive value (%)	62*	84	47	93	79
Overall accuracy (%)	70*	85	50	90	88

NHL = non-Hodgkin's lymphoma; Δ = increment; Epo = erythropoietin; O/P Epo = ratio of observed-to-predicted Epo; sTfR = soluble transferrin receptor; Hb = hemoglobin; retic = reticulocytes.

*: Although the algorithm proposed by Ludwig primarily identifies non-responders, sensitivity, specificity and positive and negative predictive values are given for identification of response, as is the case for the other algorithms.

who will respond) and specificity (how well the algorithm excludes all those who will fail), and thus their overall efficacy, vary considerably. In the study conducted by Ludwig (Ludwig et al. 1994), when one tries primarily to identify non-responders instead of responders, sensitivity and overall accuracy can be increased from 42% and 70% to 76% and 86%, respectively. Overall accuracy is not improved by doing so in the study conducted by Henry in patients receiving chemotherapy, because enhanced sensitivity (54%) is compensated by diminished specificity (52%). 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 (at least in hematologic malignancies) together with some early indicators of erythropoietic marrow response (changes in hemoglobin or sTfR). The following scheme can be proposed in practice (Fig. 8). Baseline serum Epo should be measured at baseline in patients with hematologic malignancies: treatment should not be initiated if endogenous serum Epo is above 100 mU/mL (or 200 mU/mL in severely anemic patients) or the O/P ratio is >0.9. Erythropoietic response should be

Fig. 8. Practical use of algorithms for prediction of response in cancer patients treated with rHuEpo, based on baseline endogenous Epo level and an early (2-wk) indicator of increased erythropoietic activity. The first step (baseline Epo) could be omitted in solid tumor patients. The only difference between untransfused and transfused patients is that the 2-wk Hb increment cannot be used in transfusion-dependent patients and must be replaced by the 2-wk sTfR increment

assessed after 2 weeks. In untransfused patients, if the Hb has increased by at least 0.5 g/dL, continue treatment; otherwise double the dose and definitively discontinue rHEpo after 2 additional weeks if Hb has not increased by at least 0.3 g/dL. In transfused patients, if sTfR has increased by at least 20%, continue treatment; otherwise double the dose and definitively discontinue rHEpo after 2 additional weeks if sTfR has not increased by at least 20%. It is, of course, critical that all preventable causes of failure are identified prospectively and corrected, or else no predictive model will be valid. In particular this includes vigorous iron supply and energetic treatment of intercurrent complications such as infections and bleeding.

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Chapter XVI

rhEPO in hematopoietic stem cell mobilization, transplantation and in-vitro expansion

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Summary

Various hematopoietic growth factors and cytokines are being increasingly studied in the transplant setting. They are used, not only to accelerate haematopoietic recovery after cytopenias but also as mobilizers of stem cells in donors, *ex vivo* expansion of stem cells and for supportive treatment during infections. All these new factors, alone or in combination, may contribute to improved regimens during transplantation. Bone marrow transplant (BMT) or peripheral blood progenitor stem cells transplant (PBSCT) recipients have in the period following transplantation a frequent need for red blood cell transfusions and, therefore, an increased risk of blood-transmitted infections. The anemia is caused mainly by myelosuppression after high-dose chemotherapy but an impaired erythropoietin (EPO) production and an inappropriate EPO response may also contribute. Since recombinant human erythropoietin (rhEPO) has been established as a treatment for renal anemia it has been of interest whether treatment may be of benefit in the transplantation setting. So far data do *not* support any transfusional benefits with the use of rhEPO after autologous transplantation. In patients receiving an allograft, especially patients with immune hemolysis after transplantation, rhEPO treatment seems to accelerate erythroid engraftment, increase hemoglobin levels, reduce red blood cell transfusions and shorten time to transfusion independence. However, the optimal dose of rhEPO, the route of administration, the most effective combination with other hematopoietic growth factors, and in which patient populations cost-effective rhEPO therapy is justified are still open questions.

Background