ESO Scientific Updates, Vol. 6
Anaemia in Cancer
C. Bokemeyer and H. Ludwig, editors

Prediction of Response to rHuEPO

Yves Beguin

Research Director of the National Fund for Scientific Research (FNRS, Belgium)
Department of Medicine, Division of Haematology, University of Liège, Liège, Belgium

Introduction

Patients with solid tumours or haematological malignancies often present with anaemia at diagnosis or develop it in the course of their disease [1-4]. Many studies have shown that recombinant human erythropoietin (rHuEPO) therapy can ameliorate the anaemia associated with cancer and chemotherapy, reduce the need for transfusions and improve quality of life [4]. However, many patients do not respond even to very high doses of rHuEPO. It is therefore important to be able to recognise and correct conditions which adversely affect the response to rHuEPO, in particular functional iron deficiency. When no such particular condition can be identified, the use of predictive response algorithms becomes essential. Patients can thus be selected on the basis of the likelihood of their responding to treatment and prolonged ineffective use of an expensive medication can be avoided in those patients with a low probability of response. This chapter will review factors potentially affecting the response to rHuEPO and discuss the use of predictive algorithms.

Factors influencing response to rHuEPO

Treatment schedules and criteria for response

Marked differences among studies in the rate of response to rHuEPO reflect differences in disease- and treatment-related factors, but also variations 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

Address for correspondence: Y. Beguin, University of Liège, Department of Haematology, CHU Sart-Tilman, 4000 Liège, Belgium. Tel.: +32-4-3667690, fax: +32-4-3668855, e-mail: yves.beguin@chu.ulg.ac.be

administration has been shown to ensure more favourable pharmacokinetics, resulting in higher efficacy in renal failure patients [5]. Most trials administered rHuEPO thrice weekly, a schedule demonstrated to be more efficient than daily injections in normal subjects [6]. 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 treatment [7]. 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 [8]. The response rate can thus be further improved when patients are treated for six months or more [9].

The patient's haematological parameters at baseline are also important. Patients with more severe anaemia and a greater transfusion requirement presumably have a lower probability of achieving a target haematocrit (Hct) value. Pretreatment Hct was an important factor when rHuEPO was given for the prevention of anaemia [10] but it was no longer so when it was given after anaemia was well established [11]. This has been illustrated very well in animal studies in which rHuEPO was much more "efficient" when it was started before the administration of 5-FU, being more effective at increasing the Hct before the onset of myelosuppression [12].

Trials employing less stringent criteria for defining response are likely to report better outcomes. Uniform response criteria can thus be proposed for transfused and untransfused cancer patients, whether they be severely anaemic or not. Complete response is defined by normalisation of the Hct. Major response can be defined by the removal of the need for transfusion *and* a Hct increment greater than six percentage points *and* achievement of a Hct higher than 30%. Minor response corresponds to only one of the latter two criteria or a reduction of the transfusion requirement by at least 50%. When rHuEPO is given to prevent anaemia during chemotherapy, complete response can be defined by maintenance of a normal Hct, major response by a decrease in Hct by less than six percentage points, and minor response by a larger decrease in Hct without the need for transfusion.

Disease-associated factors

A number of mechanisms can be involved in the pathogenesis of anaemia associated with cancer [1-3] and it may therefore be difficult to identify a single causative factor in an individual patient. Red cell loss may result from hypersplenism, blood loss following haemorrhage or iatrogenic phlebotomy, and autoimmune or microangiopathic haemolysis. Red cell production may be diminished by bone marrow infiltration, marrow necrosis, haemophagocytosis, myelofibrosis, deficiency of erythropoietic cofactors (folic acid, vitamin B12, iron), or infections. These mechanisms of anaemia are much more prevalent in haematological malignancies, but it is always important to identify them because specific therapeutic interventions can often be effective. However, cancer-

associated anaemia is frequently delineated by the more general features of the so-called anaemia of chronic disorders (ACD). ACD is characterised by inadequate production of erythropoietin, inhibition of the proliferation of erythroid progenitor cells in the bone marrow, and iron utilisation disturbances [1,13].

Except when there is major invasion by cancer cells and limited residual normal haematopoiesis, tumour involvement of the marrow does not appear to limit the efficacy of rHuEPO [7,14]. The type of tumour generally does not influence the response rate, provided that no other specific mechanism of anaemia is at work. Patients with multiple myeloma or low-grade lymphoma appear to have similar response rates [15,16]. Although there were no apparent differences between haematological and non-haematological malignancies in the largest study published [7], other studies suggested that patients with breast or colon cancer [17] but not those with squamous cell carcinoma [18] may respond less well than patients with myeloma.

Chemotherapy-related factors

Anaemia 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 production [19]. Patients who were heavily pretreated with chemotherapy usually experience severe stem cell damage that considerably interferes with their response to rHuEPO. Indeed, this is clearly indicated by the poorer response obtained in patients with lower platelet counts [15,16].

For patients treated concomitantly with chemotherapy and rHuEPO there is no marked difference between those receiving platinum-based regimens [20,21] and those receiving other forms of chemotherapy [15,16,22]. In the largest study published to date [7] patients receiving platinum-based chemotherapy responded more rapidly to rHuEPO than those receiving other combinations but the overall response rate was similar in the two groups. However, the 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 equally well as those not receiving concomitant chemotherapy [7]. It is, however, likely that more intensive chemotherapy regimens would be associated with lower response rates. Finally, complications of chemotherapy, such as inflammation, infections, nutritional deficiencies or bleeding, may have a negative impact on the response to rHuEPO.

Functional iron deficiency

Functional iron deficiency is a major factor limiting the efficacy of rHuEPO therapy. It is defined as an imbalance between iron requirement in the erythroid marrow and iron supply, which depends on the level of iron stores and the rate of their mobilisation. This may occur even in the presence of large iron

stores when storage iron release is impaired, as is the case in anaemia of chronic disorders [23]. Functional iron deficiency is best diagnosed by a percentage of hypochromic red cells greater than 10% [24], a parameter that is calculated by certain automated haematological cell counters. Alternatively, functional iron deficiency can be suspected when the transferrin saturation falls below 20%. As there is some concern that tumour cells may need iron for optimal growth [25], routine iron supplementation, either oral or intravenous, in all cancer patients receiving rHuEPO is not recommended. However, this should be balanced against 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 anaemia of chronic disorders. Otherwise, iron supplements can be given when the transferrin saturation is below 20% or the percentage of hypochromic red cells is greater than 10%; the supplementation should be discontinued as soon as these values return to normal. The oral route is much less effective and intravenous administration of 200 mg elemental iron every week or every other week is the treatment of choice. This will ensure the best utilisation of any given dose of rHuEPO.

Predictive models

Since the response rate to rHuEPO varies considerably among patients treated similarly and the clinical efficacy can only be assessed after several weeks of treatment, identification of early predictors of response would be of major interest. The use of such prognostic factors of response could help to give the greatest possible number of anaemic cancer patients the benefits of rHuEPO while avoiding prolonged ineffective use of an expensive medication.

A predictive algorithm of response to rHuEPO has first been proposed in the setting of anaemia associated with renal failure [26]. The best prediction by baseline parameters only was obtained with pretreatment soluble transferrin receptor (sTfR) and fibrinogen. Serum sTfR can now be measured by a commercial immunoassay and represents a quantitative measure of erythropoietic activity. There was a 100% response rate when both sTfR and fibrinogen were low, against only 29% when they were both high, and 67% when one was low and the other high. Changes in sTfR after two weeks of treatment were also predictive. When the two-week sTfR increment was ≥20%, the response rate was 96%. When the sTfR increment was <20%, the response rate was 100% when baseline sTfR was low and fibrinogen normal, 12% when baseline fibrinogen was high, and 62% when baseline fibrinogen was normal but baseline sTfR high. These prognostic factors illustrate the importance of the early erythropoietic response (changes in 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 should be more likely to respond to rHuEPO than those with adequate serum EPO levels relative to their degree of anaemia. However, studies in patients with solid tumours 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 [7,21,27,28]. As EPO levels must be interpreted in relation to the degree of anaemia, the ratio of observed to predicted EPO levels (O/P ratio) represents a better measure of the adequacy of EPO production [29]. In patients with haematological malignancies it has been observed that low baseline serum EPO levels [11] or a decreased O/P ratio [22] is associated with a significantly higher probability of response. This has been confirmed in large multicentre trials in patients with multiple myeloma or non-Hodgkin's lymphoma [15,16]. 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 [30]. In addition, in patients treated with chemotherapy serum EPO should be evaluated just prior to chemotherapy for its interpretation to be valid. Indeed, measuring serum EPO after chemotherapy may yield elevated levels compared to pre-chemotherapy values, without any change in Hct [31].

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 [11] 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-evaluable.

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 haemoglobin (Hb) levels often predicted a high probability of later response [11,16, 32]. An increase in reticulocyte counts by ≥40,000/μl from baseline to week 2 or 4 appeared to be predictive of response but its discriminative power was weak [32]. In several studies the haematological response to rHuEPO was strongly associated with early increases in sTfR levels after one to two weeks of treatment [22,28,30]. Ludwig [11] conducted the most thorough analysis and found that increases in Hb, sTfR and reticulocytes as well as decreases in 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 tumours or

haematological malignancies [11], if after two weeks of therapy EPO was >100 mU/ml and Hb had not increased by at least 0.5 g/dl there was a 94% likelihood of unresponsiveness; otherwise response was likely in 80% of the patients (Table 1). If serum EPO was <100 mU/ml and the Hb concentration had increased by ≥0.5 g/dl, the probability of response was 100%; otherwise the probability of failure was 62%. However, 34/80 patients did not fall into either of these categories and thus the prediction was valid only in just over half of them. The predictive value of a decrease in serum EPO levels could be explained in two ways. Endogenous serum EPO decreased as the Hct rose in responders, but the magnitude of the Hct changes by two weeks seemed 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 were thus more likely to have inappropriate increases in endogenous serum EPO values [31]. On the other hand, EPO could be utilised by the stimulated marrow, but this has been contradicted by many experimental data [33,34]. Alternatively, a serum ferritin value ≥400 ng/ml after two weeks predicted non-response in 88% of cases, whereas serum ferritin levels <400 ng/ml predicted response in 72% of cases. However, the specific cutoff of 400 ng/ml cannot be applied to other patients because much depends on the previous transfusion history.

Table 1. Prediction of response in patients with the anaemia of cancer treated with rHuEPO. Based on the study by Ludwig et al. [11]

Parameter at week 2		Patients	Response (%)	
Serum EPO (mU/ml)	Hb increment (g/dl)	No.	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 = haemoglobin.

Table 2. Prediction of response in patients with the anaemia of cancer not receiving chemotherapy and treated with rHuEPO. Based on the study by Henry et al. [32]

Parameter at week 2		Patients	Response (%)	
Hb increment (g/dl)	Retic increment (/μl)	No.	Yes	No
≥ 0.5	≥ 40,000	11	91	9
≥ 0.5	< 40,000	14	36	64
< 0.5	≥ 40,000	6	17	83
< 0.5	< 40,000	23	4	96

Response = haematocrit increment ≥6%. Overall response rate = 31%.
Hb = haemoglobin; retic = reticulocyte.

In a subset of patients from a large multicentre study [7] some prediction of response could be derived from changes observed in reticulocytes and Hb from baseline to week 2 of therapy [32]. Among patients not receiving chemotherapy (Table 2) the response rate was poor when the two-week increment in Hb level was <0.5 g/dl, whereas it was excellent when the Hb level and reticulocyte count increased by ≥0.5 g/dl and ≥40,000/μl, respectively. The predictive power of these parameters was much less substantial when the Hb increased 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 (Table 3). Although some improvement in response prediction could be obtained in patients with a Hb increase of ≥1 g/dl after four weeks of treatment, predicting response on the basis of the response itself may appear to be trivial.

Table 3. Prediction of response in patients with the anaemia of cancer receiving chemotherapy and treated with rHuEPO. Based on the study by Henry et al. [32]

Parameter at week 2		Patients	Response (%)	
Hb increment (g/dl)	Retic increment (/μl)	No.	Yes	No
≥ 0.5	≥ 40,000	21	67	33
≥ 0.5	< 40,000	29	66	34
< 0.5	≥ 40,000	20	50	50
< 0.5	< 40,000	62	48	52

Response = haematocrit increment ≥6%. Overall response rate = 55%.
Hb = haemoglobin; retic = reticulocyte.

Predictive algorithms based on baseline parameters and early changes

A combination of baseline parameters and early changes observed after two weeks of rHuEPO may provide another useful approach. Among evaluable patients treated in a large multicentre study [16] 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 Hb increment by week 2 was <0.3 g/dl (Table 4). On the other hand, the success rate was around 90% when baseline serum O/P EPO was less than 0.9 and Hb increased by ≥0.3 g/dl. In another large single-centre study [30] the combined use of baseline serum EPO and the two-week increase in sTfR proved to be very powerful (Table 5). Only 18% of patients with 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 two-week sTfR increment was less than 25%. Conversely, the response rate was 96% in patients with low baseline serum EPO and a substantial sTfR elevation.

Table 4. Prediction of response in patients with anaemia associated with multiple myeloma or non-Hodgkin's lymphoma and treated with rHuEPO. Based on the study by Cazzola et al. [16]

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

Response = Hb increment ≥2 g/dl. Overall response rate = 65%.
O/P EPO = ratio of observed-to-predicted serum erythropoietin; Hb = haemoglobin.

Table 5. Prediction of response in patients with the anaemia of cancer treated with rHuEPO. Based on the study by Cazzola et al. [30]

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

Response = Hb increment ≥2 g/dl. Overall response rate = 58%.
EPO = erythropoietin; sTfR = soluble transferrin receptor.

Applicability of predictive factors

There are a number of theoretical reasons why some or all of these parameters are not valid in certain situations (Table 6). While evaluation of endogenous

Table 6. 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 anaemia			
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 anaemia			
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 = haemoglobin; 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)

EPO production may be relevant in various forms of anaemia, it is irrelevant in subjects where the aim of rHuEPO therapy is to prevent anaemia that is not yet present, in those in whom better tumour oxygenation before radiotherapy or induction of fetal Hb is sought, or in disorders characterised by universal EPO deficiency. In patients with haematological malignancies [11,15,16,30], low baseline serum EPO levels or a low ratio of observed to predicted EPO levels (O/P ratio) were associated with a significantly higher probability of response, but this was usually not the case in patients with solid tumours [7,21]. On the other hand, Hb increments after two weeks of treatment may be relevant in steady-state patients but are of little help in transfused patients and in those in whom rHuEPO is intended to prevent the occurrence of severe anaemia but cannot avert some decrease in Hb 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 the output of shift reticulocytes rather than true expansion of erythropoiesis, and are therefore often not a good indicator of response [11,26]. Although sTfR levels represent the best quantitative measurement of total erythropoietic activity, they may also increase secondary to functional iron deficiency [35]. 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 Hct [31]. Assessment of changes in erythropoietic activity should be made at similar time points in the chemotherapy cycle, ideally just before administration of the next cycle, often at three to four-week intervals instead of two-week intervals. In addition, residual marrow function and the relative intensity of chemotherapy may be of great importance.

Conclusion

Several algorithms have been proposed to predict the response to rHuEPO in patients with the anaemia of cancer (Table 7). 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 considerably. In the study conducted by Ludwig [11], where primarily non-responders instead of responders were identified, the sensitivity and overall accuracy increased from 42% and 70% to 76% and 86%, respectively. The overall accuracy was not improved by doing so in the study conducted by Henry in patients receiving chemotherapy, because the increased sensitivity (54%) was 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 the as-

Table 7. Comparison of various algorithms for prediction of response to rHuEPO

Author	Ludwig [11]	Henry [32]	Henry [32]	Cazzola [16]	Cazzola [30]
No. 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 ≥40,000/μl *and* Δ Hb ≥ 0.5 g/dl	Response if 2-week Δ retic ≥ 40,000/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 = haemoglobin; retic = reticulocytes.
*Although the algorithm proposed by Ludwig primarily identifies non-responders, the sensitivity, specificity and positive and negative predictive values are given for identification of response, as is the case for the other algorithms.

sessment of the adequacy of endogenous EPO production with (some) early indicators of erythropoietic marrow response (changes in Hb or sTfR).

References

1 Means RT Jr, Krantz SB. Progress in understanding the pathogenesis of the anemia of chronic disease. Blood 1992; 80: 1639-47
2 Beguin Y. Erythropoietin and the anemia of cancer. Acta Clin Belg 1996; 51: 36-52
3 Moliterno AR, Spivak JL. Anemia of cancer. Hematol Oncol Clin North Am 1996; 10: 345-63
4 Groopman JE, Itri LM. Chemotherapy-induced anemia in adults: incidence and treatment [published erratum appears in J Natl Cancer Inst 2000 ; 92(6): 497]. J Natl Cancer Inst 1999; 91: 1616-34
5 Paganini EP, Eschbach JW, Lazarus JM, et al. Intravenous versus subcutaneous dosing of epoetin alfa in hemodialysis patients. Am J Kidney Dis 1995; 26: 331-40
6 Breymann C, Bauer C, Major A, et al. Optimal timing of repeated rh-erythropoietin administration improves its effectiveness in stimulating erythropoiesis in healthy volunteers. Br J Haematol 1996; 92: 295-301
7 Abels RI. Use of recombinant human erythropoietin in the treatment of anemia in patients who have cancer. Semin Oncol 1992; 19: 29-35
8 Beguin Y, Loo M, R'Zik S, et al. Quantitative assessment of erythropoiesis in haemodialysis patients demonstrates gradual expansion of erythroblasts during constant treatment with recombinant human erythropoietin. Br J Haematol 1995; 89: 17-23
9 Henry DH, Abels RI. Recombinant human erythropoietin in the treatment of cancer and chemotherapy-induced anemia: Results of double-blind and open-label follow-up studies. Semin Hematol 1994; 21 (suppl 3): 21-8
10 Crawford J, Blackwell S, Shoemaker D, et al. Prevention of chemotherapy related anemia by recombinant human erythropoietin (EPO) in patients with small cell lung cancer (SCLC) receiving cyclophosphamide, doxorubicin, and etoposide (CAE) chemotherapy with G-CSF support. Blood 1994; 84 (suppl 1): 129a (abstract)
11 Ludwig H, Fritz E, Leitgeb C, Pecherstorfer M, Samonigg L, Schuster J. Prediction of response to erythropoietin treatment in chronic anemia of cancer. Blood 1994; 84: 1056-63
12 Matsumoto T, Endoh K, Kamisango K, et al. Effect of recombinant human erythropoietin on anticancer drug-induced anaemia. Br J Haematol 1990; 75: 463-8
13 Sears D. Anemia of chronic disease. Med Clin North Am 1992; 76: 567-79
14 Oster W, Herrmann F, Gamm H, et al. Erythropoietin for the treatment of anemia of malignancy associated with neoplastic bone marrow infiltration. J Clin Oncol 1990; 8: 956-62
15 Osterborg A, Boogaerts MA, Cimino R, et al. Recombinant human erythropoietin in transfusion-dependent anemic patients with multiple myeloma and non-Hodgkin's lymphoma. A randomized multicenter study. Blood 1996; 87: 2675-82
16 Cazzola M, Messinger D, Battistel V, et al. Recombinant human erythropoietin in the anemia associated with multiple myeloma or non-Hodgkin's lymphoma: dose finding and identification of predictors of response. Blood 1995; 86: 4446-53
17 Ludwig H, Fritz E, Leitgeb C, et al. Erythropoietin treatment for chronic anemia of selected hematological malignancies and solid tumors. Ann Oncol 1993; 4: 161-7
18 Ludwig H, Pecherstorfer M, Leitgeb C, Fritz E. Recombinant human erythropoietin for the treatment of chronic anemia in multiple myeloma and squamous cell carcinoma. Stem Cells 1993; 11: 348-55
19 Wood PA, Hrushesky WJ. Cisplatin-associated anemia: an erythropoietin deficiency syndrome. J Clin Invest 1995; 95: 1650-9

20 Markman M, Reichman B, Hakes T, et al. The use of recombinant human erythropoietin to prevent carboplatin-induced anemia. Gynecol Oncol 1993; 49: 172-6
21 Cascinu S, Fedeli A, Del Ferro E, Luzi Fedeli S, Catalano G. Recombinant human erythropoietin treatment in cisplatin-associated anemia: a randomized, double-blind trial with placebo. J Clin Oncol 1994; 12: 1058-62
22 Cazzola M, Ponchio L, Beguin Y, et al. Subcutaneous erythropoietin for treatment of refractory anemia in hematologic disorders. Results of a phase I/II clinical trial. Blood 1992; 79: 29-37
23 Fillet G, Beguin Y, Baldelli L. Model of reticuloendothelial iron metabolism in humans: abnormal behavior in idiopathic hemochromatosis and in inflammation. Blood 1989; 74: 844-51
24 Macdougall IC, Cavill I, Hulme B, et al. Detection of functional iron deficiency during erythropoietin treatment: a new approach. Br Med J 1992; 304: 225-6
25 Weinberg ED. The role of iron in cancer. Eur J Cancer Prev 1996; 5: 19-36
26 Beguin Y, Loo M, R'Zik S, et al. Early prediction of response to recombinant human erythropoietin in patients with the anemia of renal failure by serum transferrin receptor and fibrinogen. Blood 1993; 82: 2010-6
27 Platanias LC, Miller CB, Mick R, et al. Treatment of chemotherapy-induced anemia with recombinant human erythropoietin in cancer patients. J Clin Oncol 1991; 9: 2021-6
28 Ponchio L, Beguin Y, Farina G, et al. Evaluation of erythroid marrow response to recombinant human erythropoietin in patients with cancer anaemia. Haematologica 1992; 77: 494-501
29 Beguin Y, Clemons G, Pootrakul P, Fillet G. Quantitative assessment of erythropoiesis and functional classification of anemia based on measurements of serum transferrin receptor and erythropoietin. Blood 1993; 81: 1067-76
30 Cazzola M, Ponchio L, Pedrotti C, et al. Prediction of response to recombinant human erythropoietin (rHuEpo) in anemia of malignancy. Haematologica 1996; 81: 434-41
31 Beguin Y, Clemons GK, Oris R, Fillet G. Circulating erythropoietin levels after bone marrow transplantation: Inappropriate response to anemia in allogeneic transplants. Blood 1991; 77: 868-73
32 Henry D, Abels R, Larholt K. Prediction of response to recombinant human erythropoietin (r-huepo/epoetin-alpha) therapy in cancer patients [letter]. Blood 1995; 85: 1676-8
33 Naets JP, Wittek M. Effect of erythroid hypoplasia on utilization of erythropoietin. Nature 1965; 206: 726-7
34 Piroso E, Erslev AJ, Flaharty KK, Caro J. Erythropoietin life span in rats with hypoplastic and hyperplastic bone marrows. Am J Hematol 1991; 36: 105-10
35 Huebers HA, Beguin Y, Pootrakul P, Einspahr D, Finch CA. Intact transferrin receptors in human plasma and their relation to erythropoiesis. Blood 1990; 75: 102-7