LEADING ARTICLE

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The Clinical Value of Erythropoietin in Patients with Cancer

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Abstract

Erythropoietin has been successfully used in the treatment of cancer-related anaemia. About two-thirds of patients with the 'anaemia of chronic disorders', anaemia due to neoplastic bone marrow infiltration or therapy-related anaemia, are expected to respond to high doses of erythropoietin with a haemoglobin increase of at least 2 g/dl. In the myelodysplastic syndromes, about one-third of patients will show a response when very high doses of erythropoietin are combined with granulocyte colony-stimulating factor. The response to erythropoietin is slow, requiring several months to develop. Various factors have been reported to predict a response, but the prediction models proposed are contradictory and have not been prospectively validated. Therefore, the most common strategy to determine the responsiveness of cancer-related anaemia to erythropoietin is to subject the patient to a treatment trial of several months' duration.

Treatment with erythropoietin needs to be compared with the transfusion of red blood cells, which has similar effects on the patient's haemoglobin level. Erythropoietin is a generally well tolerated drug, but it is slow to exert an effect and ineffective in a substantial proportion of patients. Red blood cell transfusion is associated with a small risk of infectious, allergic or toxic complications, but it leads to a rapid haemoglobin increase in virtually all patients treated. Cost and cost-benefit analyses from several countries indicate that, in patients with cancer-related anaemia, treatment with erythropoietin is considerably more expensive than the transfusion of allogeneic red blood cells. Thus, the choice between the two treatment options will be influenced by the financial resources of the respective healthcare systems.

The haematopoietic growth factor erythropoietin regulates the proliferation and maturation of red blood cells, which are required for the transport of oxygen from the lungs to the peripheral organs and tissues.[1] Since erythropoietin became available as a recombinant protein some 15 years ago, it has been widely used in patients with different types of anaemia, including renal anaemia, the anaemia of inflammation, and cancer-related anaemia.

Erythropoietin exerts its effects by increasing the number of erythrocytes. The resulting increase in the capacity for oxygen transport may lead to an improved quality of life. An increased oxygen supply to tumours may slow their progression because hypoxia has been postulated to favour the development of genetic instability and the formation of a fragile vasculature facilitating tumour spread.[2] Finally, increased tumour oxygenation may en-

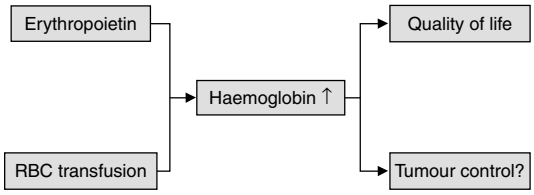

Fig. 1. Effects of erythropoietin and red blood cell (RBC) transfusion on the patient: crucial role of haemoglobin increase (↑).

hance the efficacy of oxygen-dependent modes of therapy, such as radiotherapy (figure 1).[2]

The actions of erythropoietin in cancer patients appear to be solely related to its effects on erythropoiesis (figure 2). Non-erythropoietic effects, which have recently been demonstrated in the central nervous system,[3] have so far not been observed in patients with cancer. Therefore, the net effect of erythropoietin must be compared with that of blood transfusion, which also increases the number of circulating erythrocytes.

The transfusion of red blood cells from an allogeneic donor is the most efficient way to increase the red blood cell mass, with a rapid increase in haemoglobin level of approximately 1 g/dl per unit of blood transfused.[5,6] With the current donor-screening programmes and preparative procedures, the risk of serious infectious or allergic reactions is small (table I). In patients with long-term transfusion dependency, iron overload has to be considered. To be clinically relevant, it requires the transfusion of at least 50 units of blood (corresponding to 10g of iron). Whether allogeneic blood transfusion induces a state of immunosuppression favouring tumour growth remains controversial.[7,8] The frequency of adverse transfusion effects can be reduced by leucocyte-depletion filters, which are routinely used in a growing number of countries.[8]

Although in the past decade erythropoietin has been studied intensively in cancer patients, it has never been compared with red blood cell transfusion in a randomised trial with equal haemoglobin target levels in both patient groups. The studies summarised in the following sections compared the effects of erythropoietin with those of a 'standard treatment' that aimed to maintain much lower haemoglobin levels than those targeted in the group of patients receiving erythropoietin.

1. Causes of Cancer-Related Anaemia

Cancer-related anaemia may be due to haemorrhage, haemolysis or insufficient production of red blood cells in the bone marrow.[9-11] It is the last-named category that benefits from erythropoietin therapy. There are four major causes of insufficient erythrocyte production in cancer patients: (i) incompletely understood immunological mechanisms leading to the 'anaemia of chronic disorders'; (ii) infiltration of neoplastic cells into the bone marrow; (iii) therapy-related myelosuppression; and (iv) inefficient erythropoiesis in the setting of myeloid malignancies, in particular in the myelodysplastic syndromes. In all four types of cancer-related erythropoietic hypoproliferation, the mechanisms that eventually lead to anaemia are complex.[9-11] Among others, they include inadequately low serum erythropoietin levels in the anaemia of chronic disorders and in therapy-related

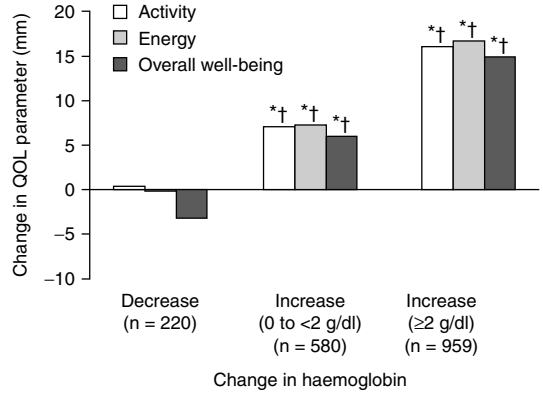

Fig. 2. Effects of erythropoietin therapy on quality of life (QOL) as determined by rating ability to perform daily activities, energy level, and overall well-being on a 100mm linear analogue scale: dependency of QOL improvement on haemoglobin increase (reproduced with permission from Lippincott Williams & Wilkins©[4]). * Indicates significantly different from baseline ($p < 0.01$); † indicates significantly different from adjacent haemoglobin change group ($p < 0.01$).

Table I. Risks of severe infectious or allergic complications of blood transfusion[5]

Complication	Estimated frequency per unit of blood transfused
Hepatitis B	1 : 30 000 – 1 : 250 000
Hepatitis C	1 : 30 000 – 1 : 150 000
Human immunodeficiency virus infection	1 : 200 000 – 1 : 2 000 000
Acute haemolytic reactions	1 : 250 000 – 1 : 1 000 000

anaemia; inhibition of erythropoietin by other cytokines in the anaemia of chronic disorders and anaemia due to neoplastic bone marrow infiltration; and a decreased responsiveness to erythropoietin of abnormal erythropoietic precursor cells in the myelodysplastic syndromes.[9,12] In many patients, two or more reasons for an insufficient production of red blood cells are present at the same time.

2. Practical Aspects: Dosage, Administration Schedule, Duration of Therapy

Phase I studies in cancer patients with the anaemia of chronic disorders, therapy-related anaemia or anaemia due to neoplastic bone marrow infiltration showed plateau haemoglobin responses at weekly erythropoietin doses of 500 to 1500 U/kg bodyweight given intravenously or subcutaneously.[13-16] For the somewhat more efficient subcutaneous route of administration, the most frequently used schedule in subsequent phase II, III and IV studies consisted of three injections of 150 U/kg each per week (for an average-weight adult patient: 3 x 10 000U subcutaneously); this dosage was doubled if no response was obtained after 4 to 8 weeks of therapy. To counteract functional iron deficiency, which is often present in cancer patients, concomitant oral or intravenous administration of iron is recommended.[10]

Anaemia in patients with myelodysplastic syndromes rarely responds to the range of erythropoietin dosages used in other cancer patients.[9] In most studies, weekly doses of 70 000 to 140 000U, often in combination with other growth factors, have been used.

In comparison with the immediate haemoglobin increase following the transfusion of red blood cells, the response to erythropoietin is slow (figure 3). Therefore, a treatment trial of at least 2 months' duration has been recommended to determine the responsiveness of anaemia in a patient to erythropoietin.[17]

According to a recent publication, a single weekly injection of 40 000U of erythropoietin may have the same efficacy as three divided doses of 10 000U each per week.[19] Even more infrequent applications may be possible using the erythropoietin derivative darbepoetin alfa, which has a longer half-life than conventional erythropoietin. Darbepoetin alfa showed promising activity in preliminary studies in cancer patients with the anaemia of chronic disorders or chemotherapy-related anaemia.[20,21] However, these reports have to be interpreted with caution because no data have yet been presented from randomised trials directly comparing different erythropoietin derivatives or different schedules of administration.

3. Treatment Results

Four different groups of patients may be distinguished in whom erythropoietin has been used to

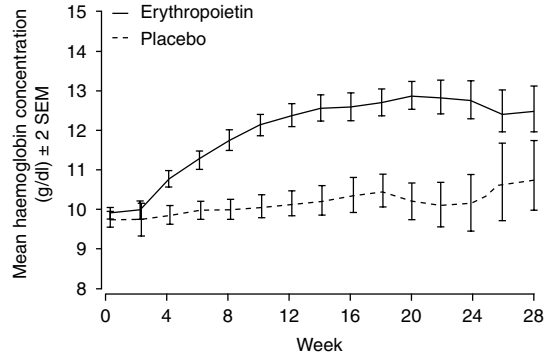

Fig. 3. Temporal development of haemoglobin response in patients treated with erythropoietin (n = 251) versus placebo (n = 124) [reproduced with permission from Lippincott Williams & Wilkins©[18]]. **SEM** = standard error of mean.

Table II. Effects of erythropoietin therapy on haemoglobin levels and transfusion requirements in patients with non-myeloid malignancies and anaemia undergoing chemotherapy: results of randomised phase III studies[a]

Study	Treatment	No. of pts	Dose per week (U/kg)[b]	Treatment duration (wks)	Responders (%)[c]	Mean haemoglobin increase (g/dl)	Patients transfused (pre- →post-therapy) [%]	Mean number of RBC units transfused per patient per month (pre- → post-therapy)
Non-platinum chemotherapy								
Abels[23]	Placebo	74		12	14	0.4	27 →37[d]	0.7 →0.8[d]
	Erythropoietin	79	450	12	58	2.3	25 →29[d]	0.7 →0.5[d]
Littlewood et al.[18]	Placebo	124		12-24	19	0.5	36 →40	0.8
	Erythropoietin	251	450 →900	12-24	71	2.2	28 →25	0.5
Cisplatin chemotherapy								
Abels[23]	Placebo	61		12	7	0.4	44 →56[d]	1.2 →1.0[d]
	Erythropoietin	64	450	12	48	2.0	44 →27[d]	1.7 →0.6[d]
Cascinu et al.[22]	Placebo	50		9	2[e]	–0.6	56	0.9
	Erythropoietin	50	300	9	82[e]	1.9	20	0.2
Multiple myeloma								
Garton et al.[26]	Placebo	10		12	0	NI	NI	NI
	Erythropoietin	10	450 →900	12	70	NI	NI	NI
Dammacco et al.[25]	Placebo	76		12	9	0.0	37 →47	NI
	Erythropoietin	69	450 →900	12	58	1.8	36 →28	NI
Paediatric patients								
Porter et al.[24]	Placebo	10		16	NI	NI	0 →100	3.3
	Erythropoietin	10	450 →900	16	NI	NI	0 →90	1.1

a Patients were eligible for inclusion in the study at a haemoglobin concentration below 9.0 g/dl,[22] 10.5 g/dl[18,23,24] or 11 g/dl,[25] or a haematocrit below 30%.[26]

b → indicates followed by.

c Unless otherwise stated, response was defined as an increase in haemoglobin of 2 g/dl or an increase in haematocrit of 6%.

d Transfusion requirement during the first versus the second and third months of treatment.

e Response was defined as an increase in haemoglobin of 1 g/dl.

RBC = red blood cell; **NI** = no information.

prevent or treat cancer-related anaemia: (i) patients with solid tumours or non-myeloid haematological malignancies not undergoing myelosuppressive antineoplastic therapy; (ii) patients with such malignancies undergoing chemotherapy; (iii) patients undergoing radiotherapy; and (iv) patients with abnormal erythropoiesis in the setting of myeloid malignancies. For each group of patients, representative studies demonstrating the effects of erythropoietin have been selected from the literature. Placebo-controlled, randomised trials were preferred to non-randomised studies. Other selection criteria included the range of diseases treated (preference for homogeneous patient cohorts), trial size (preference for large trials), and completeness of data reporting (preference for studies reporting the parameters listed in table II, table III and table IV).

3.1 Patients with Non-Myeloid Malignancies not Undergoing Myelosuppressive Antineoplastic Therapy

Few studies focus on this group of patients, whose anaemia is explained by the anaemia of chronic disorders or by neoplastic bone marrow infiltration.[23,32] Using the treatment algorithm in section 2, haematological responses (usually de-

fined as a haemoglobin increase of at least 2 g/dl) were seen in about two-thirds of patients treated in placebo-controlled randomised[23] and non-randomised trials,[32] with a reduction in the number of patients requiring transfusions by up to 50%.[32] The haemoglobin increases were associated with an improved quality of life, which was measured using questionnaires and visual scales for energy level, ability to perform daily activities and overall well-being.[23,32]

In a murine model of multiple myeloma, erythropoietin showed immune-mediated antineoplastic properties in addition to its stimulatory effects on erythropoiesis.[33] Such observations have so far not been made in myeloma patients receiving erythropoietin.[15]

3.2 Patients with Non-Myeloid Malignancies Undergoing Chemotherapy

Numerous phase II, III and IV studies have been performed in this group of patients. Approximately 50 to 70% of patients showed a haematological response with a mean haemoglobin increase of approximately 2 g/dl and a variable reduction in transfusion need (table II and table III). Erythropoietin not only improved haemoglobin levels in patients with established anaemia but, in a randomised trial in non-anaemic breast cancer patients, it prevented anaemia development when given early in the course of chemotherapy.[34] A recent meta-analysis of randomised trials showed that, on average, 4.4 patients receiving chemotherapy need to be treated with erythropoietin in order to avoid one blood transfusion.[35] Although a direct comparison was not made, treatment results appeared similar in patients with or without neoplastic bone marrow infiltration, patients on cisplatin-containing chemotherapy versus those receiving chemotherapy with other agents, or paediatric versus adult cancer patients (table II).

Increases in haemoglobin were generally associated with an improved quality of life[4,17-19,23,25] (figure 2). In addition, observations in experimental animals suggest that chemotherapy may be more efficacious at higher haemoglobin levels.[36] A recently published human trial also described a trend towards improved tumour control during erythropoietin therapy, but this did not reach statistical significance.[18]

3.3 Patients with Non-Myeloid Malignancies Undergoing Radiotherapy

The main interest in treating or preventing anaemia in patients undergoing radiotherapy is to improve tumour oxygenation.[2] Numerous retrospective studies provided compelling evidence that anaemia is associated with poor treatment outcome in patients with non-myeloid malignancies undergoing radiotherapy.[37-41] One possible ex-

Table III. Effects of erythropoietin therapy on haemoglobin levels and transfusion requirements in patients with non-myeloid malignancies and anaemia undergoing chemotherapy: results of community-based phase IV studies[a]

Study	No. of pts	Erythropoietin dose per week (U)[b]	Treatment duration (wks)	Responders (%)	Mean haemoglobin increase (g/dl)	Patients transfused (pre- →post-therapy)[c] [%]	Mean number of RBC units transfused per patient per month (pre- →post-therapy)[c]
Demetri et al.[4]	2289	3 x 10 000 →3 x 20 000	16	61	2.0	29 →5	1.0 → 0.2
Gabrilove et al.[19]	2964	1 x 40 000 →1 x 60 000	16	68	1.8	14 →5	0.4 →0.1
Glaspy et al.[17]	2030	3 x 10 000 →3 x 20 000	16	53	1.8	22 →10	0.6 →0.3

a Patients were eligible for inclusion in the study at a haemoglobin concentration below 11 g/dl.[4,19] Response was defined as an increase in haemoglobin of 2 g/dl[4,17,19] or achievement of a haemoglobin level of at least 12 g/dl.[4,19]

b → indicates followed by.

c In 42 to 53% of the patients starting erythropoietin treatment, no post-therapy values were available. The post-therapy values given pertain only to those patients completing the entire treatment period.

RBC = red blood cell.

Table IV. Effects of erythropoietin therapy alone or in combination with granulocyte colony-stimulating factor (G-CSF) on haemoglobin levels and transfusion requirements in patients with anaemia in the setting of myelodysplastic syndromes[a]

Study	Treatment	No. of pts	Dose per week (U/kg)[b]	Treatment duration (wks)	Responders (%)	Mean haemoglobin increase (g/dl)	Patients transfused (pre- →post-therapy) [%]	Mean number of RBC units transfused per patient per month (pre- →post-therapy)
Erythropoietin alone								
Hellström et al.[28]	Erythropoietin	12	600 →3000	12	17	0.1	67 →58	1.1 →1.5
Italian group[29]	Placebo	37	-	8	0	–0.3	NI	NI
	Erythropoietin	38	1050	8	13	1.7	NI	NI
Erythropoietin + G-CSF								
Negrin et al.[30]	Erythropoietin + G-CSF	24	700 →2100	16	29	1.0	92 →71	2.6 →2.0
Hellström-Lindberg et al.[31]	Erythropoietin + G-CSF	47	500 →1000	10-12	38	NI	NI	NI
Mantovani et al.[27]	Erythropoietin + G-CSF	25	600 →1200	36	56	2.2	82 →44	NI

a Patients were eligible for inclusion in the study at a haemoglobin concentration below 9 g/dl[27-29] or 10 g/dl.[30,31] Response was defined as an increase in haemoglobin of 1.5 g/dl[28,31] or 2 g/dl,[27,29,30] or complete elimination of pre-existent transfusion requirement.[27,29-31]

b → indicates followed by.

RBC = red blood cell; **NI** = no information.

planation is that low haemoglobin levels lead to poor tumour oxygenation, which in turn compromises the efficacy of radiotherapy. This interpretation is supported by animal studies demonstrating that treatment of anaemia by blood transfusion or erythropoietin improves tumour oxygenation[42,43] and partially restores the efficacy of radiotherapy.[44,45] However, these effects have only been observed in very small tumours.

In humans, the effect of correcting anaemia on the efficacy of radiotherapy is less clear. One early randomised trial in patients with cancer of the uterine cervix showed a higher local relapse rate in patients with untreated anaemia compared with patients whose anaemia was corrected by blood transfusion.[46] Methodological aspects of the analysis, however, as well as possible imbalances in patient characteristics provide alternative explanations for the observed differences. In an intention-to-treat analysis, survival was comparable in both trial arms.[47]

Increases in haemoglobin levels were observed in 60 to 80% of radiotherapy patients who received erythropoietin in the setting of randomised trials,[48,49] and the impact of erythropoietin on tumour control is currently being investigated.[50] In a retrospective study of patients undergoing radiotherapy for head and neck cancer, patients with untreated anaemia experienced a worse outcome than patients treated with erythropoietin.[51] This observation needs to be confirmed in a prospective trial.

3.4 Patients with Myelodysplastic Syndromes

Responses to erythropoietin have been observed in less than 20% of patients with anaemia due to myelodysplastic syndromes (table IV). More encouraging results were obtained when very high doses of erythropoietin were combined with low doses of granulocyte colony-stimulating factor (G-CSF), with haemoglobin increases in approximately one-third of treated patients. No consistent differences in response to erythropoietin were demonstrated between patients with the individual subtypes of myelodysplastic syndromes.

4. Prediction of Response to Erythropoietin

Two types of retrospective analysis have been performed to identify patients who may benefit from erythropoietin therapy. The first approach focused on the identification of patients with a high likelihood of developing transfusion-dependent anaemia during chemotherapy.[52-54] In one study, this included patients with leukaemia, lung cancer or pre-existing anaemia;[54] another investigation identified haemoglobin levels ≤12 g/dl before chemotherapy, poor performance status, and lymphocyte count ≤700/μl as risk factors for the development of transfusion-dependent anaemia.[53]

The second approach aimed to identify factors predicting a response in individual patients with established anaemia (table V). Most predictive models were derived from small numbers of patients and no model has been validated prospectively. For different groups of patients, different prediction schemes have been published. Models developed by one group of authors[55,56] could not always be confirmed by others.[27,57] Therefore, the overall value of these models is limited. Pre-treatment factors reported to predict a response in at least some patient groups included inadequately low serum erythropoietin levels, or freedom from transfusion requirement. Whether erythropoietic responses observed several weeks after the initiation of therapy deserve to be looked upon as 'predictive' appears questionable. This type of prediction comes close to the recommendation mentioned above to subject a patient with cancer-related anaemia to a treatment trial of sufficient duration in order to ascertain whether the anaemia will respond to erythropoietin.[4,17,25]

5. Cost and Cost-Benefit Analyses

The cost of erythropoietin therapy has been compared with that of red blood cell transfusion in patients with anaemia induced by radiotherapy or chemotherapy. Although the analyses summarised in table VI varied with respect to data source and methodology used, their conclusions were identical. Irrespective of the care system analysed, the cost of erythropoietin therapy was substantially higher than that of blood transfusion. Whether the possible risk of transmission of Creutzfeldt-Jakob

Table V. Factors reported to predict a response to erythropoietin in cancer patients with established anaemia

Study	No. of pts	Predictive factors identified:		
		Before treatment	After 2 wks treatment	After 4 wks treatment
Myeloid and non-myeloid malignancies with or without chemotherapy				
Ludwig et al.[56]	40		Serum erythropoietin <100 U/L; haemoglobin ↑≥0.5 g/dl; serum ferritin <400 ng/ml	
Cazzola et al.[58]	48	Serum erythropoietin <100 U/L	Serum soluble transferrin receptor ↑≥25%	Haemoglobin ↑≥1 g/dl; reticulocyte count ↑≥40 000/μl
Non-myeloid malignancies with or without chemotherapy				
Henry et al.[57]	206			Haemoglobin ↑≥1 g/dl; reticulocyte count ↑≥40 000/μl
Multiple myeloma and non-Hodgkin's lymphoma with or without chemotherapy				
Cazzola et al.[16]	57	Serum erythropoietin ≤50 U/L	Haemoglobin ↑≥0.3 g/dl	
Österborg et al.[15]	121	Serum erythropoietin <50 U/L		
Myelodysplastic syndromes				
Hellström-Lindberg[59] (erythropoietin alone)	179	Serum erythropoietin ≤200 U/L; no transfusions; no RARS		
Hellström-Lindberg et al.[55] (erythropoietin + G-CSF)	98	Serum erythropoietin <100 U/L; <2 transfusions/month		

G-CSF = granulocyte colony-stimulating factor; **RARS** = refractory anaemia with ringed sideroblasts; ↑ indicates increases to.

Table VI. Prevention and treatment of anaemia in cancer patients: cost comparison between erythropoietin and red blood cell (RBC) transfusion[a]

Study	Country	Data source	Treatment cost per patient per month ($US)		
			Erythropoietin	RBC transfusion	Magnitude of difference (erythropoietin *vs* RBC transfusion) [n-fold]
Chemotherapy-related anaemia					
Sheffield et al.[62]	USA	8 published trials	2162	747	3
Ortega et al.[60]	Canada	2 published trials	1197	194	6
Barosi et al.[63]	Italy	2 published trials	1142	52	22
Meadowcroft et al.[64]	USA	174 published articles, 50 patients with breast cancer	2161	56	39
Cremieux et al.[61]	USA	4 published trials	1888	354	5
Chemoradiotherapy-related anaemia					
Kavanagh et al.[65]	USA	1 published trial, 12 patients with cervical cancer	2579	660	4

a Apart from the cost of drug acquisition (10 000U of erythropoietin were assumed to cost $94-$125), costs of erythropoietin included costs of laboratory monitoring,[60-62] pharmacy expenses,[63] iron supplementation,[62] nursing time,[62,63] physician visits,[60,62] equipment,[60,62,63] patient education,[60] fatigue,[64] treatment of non-responders with blood transfusion,[61,65] and treatment of adverse events.[62,64,65] Costs of blood transfusion were estimated on the basis of local charges,[65] local costs,[60,64] or published cost ranges.[60-63] The estimated cost of one red blood cell unit ranged from $US137 to $US422 (median $329). In addition, the costs of typing, screening and compatibility testing,[60,62,63,65] hospitalisation,[60,62] nursing time,[60,62] physician visits,[60,62] equipment,[61,62] patient time,[60] fatigue[64] and treatment of adverse events[60,62-65] were included in the analyses.

disease, and its impact on the pool of blood donors and the cost of blood products, will tilt the balance in favour of erythropoietin, remains to be seen.

No cost analysis of erythropoietin has so far been published for patients with myelodysplastic syndromes. Applying the current price of erythropoietin in the US (10 000U cost approximately $US100) to the data reported for maintenance therapy,[66] one is able to calculate that in a non-selected group of patients with myelodysplastic syndromes, one needs to spend approximately $US150 000 in order to obtain one erythropoietic response lasting 12 months.

At our present state of knowledge, the benefit resulting from erythropoietin therapy is limited to an improvement in quality of life. Two types of approaches have been used to quantify this benefit in monetary terms. In the first approach, cancer patients receiving chemotherapy were asked how much they would be willing to pay for the benefits experienced after 3 months of erythropoietin therapy.[60] Their average 'willingness-to-pay' covered less than 20% of the actual cost of erythropoietin and only 4% of patients were prepared to pay the full amount. The second approach assumes that a year of life of good quality is 'longer' than a year of life of poor quality. Quality-adjusted life years (QALYs) are calculated by multiplying the number of years of life by a quality adjuster, which is a number from 0 (dead) to 1 (perfect health).[67,68] Calculations for the price of 1 QALY gained through treatment with erythropoietin ranged from $US110 769 to $US214 391.[61,63]

6. Conclusions

Both erythropoietin and blood transfusion may be used to prevent or treat anaemia in cancer patients. Erythropoietin is well tolerated, but it is expensive, slow to exert an effect and ineffective in a substantial proportion of patients. Blood transfusion is associated with a small risk of infectious, allergic or toxic complications, but it is relatively inexpensive and highly reliable, with a prompt haemoglobin increase in virtually all patients treated. The effectiveness of blood transfusion in improving quality of life for patients has never been rigorously tested. However, it appears reasonable, however, to assume that an increase in

haemoglobin will lead to an improvement in quality of life, irrespective of whether such an increase was induced by erythropoietin or by blood transfusion.

In many patients with cancer, anaemia is a feature of advanced disease. These patients are unlikely to live long enough to experience the long-term hazards of blood transfusion. In other patients, anaemia is a transient problem caused or aggravated by cancer therapy early in the disease course. These patients require few if any blood transfusions. Therefore, the risk of incurring lasting damage is small. Treatment with erythropoietin would be particularly attractive in patients with a long life expectancy and chronic transfusion dependency, such as patients with low-risk myelodysplastic syndromes. Ironically, these patients are not very likely to respond.

Cost and cost-benefit analyses from several countries indicate that, in patients with cancer-related anaemia, erythropoietin therapy is considerably more expensive than the transfusion of allogeneic red blood cells. Thus, the choice between the two treatment options will be influenced by the financial resources of the respective healthcare systems.

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References

1. Krantz SB. Erythropoietin. Blood 1991; 77: 419-34
2. Smaniotto D, Luzi S, Morganti AG, et al. Prognostic significance of anemia and role of erythropoietin in radiation therapy. Tumori 2000; 86: 17-23
3. Cerami A. Beyond erythropoiesis: Novel applications for recombinant human erythropoietin. Semin Hematol 2001; 38 (3 Suppl. 7): 33-9
4. Demetri GD, Kris M, Wade J, et al. Quality-of-life benefit in chemotherapy patients treated with epoetin alfa is independent of disease response or tumor type: results from a prospective community oncology study. Procrit Study Group. J Clin Oncol 1998; 16: 3412-25
5. Goodnough LT, Brecher ME, Kanter MH, et al. Transfusion medicine. First of two parts—blood transfusion. N Engl J Med 1999; 340: 438-47
6. Dzieczkowski J, Anderson KC. Transfusion biology and therapy. In: Fauci AS, Braunwald E, Isselbacher KJ, et al., editors. Harrison's principles of internal medicine. New York: McGraw-Hill, 1998: 718-24
7. Busch OR, Hop WC, Hoynck van Papendrecht MA, et al. Blood transfusions and prognosis in colorectal cancer. N Engl J Med 1993; 328: 1372-6
8. Bordin JO, Heddle NM, Blajchman MA. Biologic effects of leukocytes present in transfused cellular blood products. Blood 1994; 84: 1703-21
9. Dührsen U, Hossfeld DK. Hematopoietic growth factors and the treatment of tumor-associated anemias. Ann Hematol 1994; 69: 213-21
10. Erslev AJ. Erythropoietin and anemia of cancer. Eur J Haematol 2000; 64: 353-8
11. Nowrousian MR. Recombinant human erythropoietin in the treatment of cancer-related or chemotherapy-induced anaemia in patients with solid tumours. Med Oncol 1998; 15 Suppl. 1: 19-28
12. Miller CB, Jones RJ, Piantadosi S, et al. Decreased erythropoietin response in patients with the anemia of cancer. N Engl J Med 1990; 322: 1689-92
13. 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
14. Miller CB, Platanias LC, Mills SR, et al. Phase I-II trial of erythropoietin in the treatment of cisplatin-associated anemia. J Natl Cancer Inst 1992; 84: 98-103
15. Österborg 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. The European Study Group of Erythropoietin (Epoetin Beta) Treatment in Multiple Myeloma and Non-Hodgkin's Lymphoma. 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. Glaspy J, Bukowski R, Steinberg D, et al. Impact of therapy with epoetin alfa on clinical outcomes in patients with nonmyeloid malignancies during cancer chemotherapy in community oncology practice. Procrit Study Group. J Clin Oncol 1997; 15: 1218-34
18. Littlewood TJ, Bajetta E, Nortier JW, et al. Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: results of a randomized, double-blind, placebo-controlled trial. J Clin Oncol 2001; 19: 2865-74
19. Gabrilove JL, Cleeland CS, Livingston RB, et al. Clinical evaluation of once-weekly dosing of epoetin alfa in chemotherapy patients: improvements in hemoglobin and quality of life are similar to three-times-weekly dosing. J Clin Oncol 2001; 19: 2875-82
20. Glaspy J, Jadeja JS, Justice G, et al. A dose-finding and safety study of novel erythropoiesis stimulating protein (NESP) for the treatment of anaemia in patients receiving multicycle chemotherapy. Br J Cancer 2001; 84 Suppl. 1: 17-23
21. Smith RE, Jr. , Jaiyesimi IA, Meza LA, et al. Novel erythropoiesis stimulating protein (NESP) for the treatment of anaemia of chronic disease associated with cancer. Br J Cancer 2001; 84 Suppl. 1: 24-30
22. Cascinu S, Fedeli A, Del Ferro E, et al. Recombinant human erythropoietin treatment in cisplatin-associated anemia: a

randomized, double-blind trial with placebo. J Clin Oncol 1994; 12: 1058-62
23. Abels RI. Recombinant human erythropoietin in the treatment of the anaemia of cancer. Acta Haematol 1992; 87 Suppl. 1: 4-11
24. Porter JC, Leahey A, Polise K, et al. Recombinant human erythropoietin reduces the need for erythrocyte and platelet transfusions in pediatric patients with sarcoma: a randomized, double-blind, placebo-controlled trial. J Pediatr 1996; 129: 656-60
25. Dammacco F, Castoldi G, Rodjer S. Efficacy of epoetin alfa in the treatment of anaemia of multiple myeloma. Br J Haematol 2001; 113: 172-9
26. Garton JP, Gertz MA, Witzig TE, et al. Epoetin alfa for the treatment of the anemia of multiple myeloma. A prospective, randomized, placebo-controlled, double-blind trial. Arch Intern Med 1995; 155: 2069-74
27. Mantovani L, Lentini G, Hentschel B, et al. Treatment of anaemia in myelodysplastic syndromes with prolonged administration of recombinant human granulocyte colony-stimulating factor and erythropoietin. Br J Haematol 2000; 109: 367-75
28. Hellström E, Birgegard G, Lockner D, et al. Treatment of myelodysplastic syndromes with recombinant human erythropoietin. Eur J Haematol 1991; 47: 355-60
29. Italian Cooperative Study Group for rHuEpo in Myelodysplastic Syndromes. A randomized double-blind placebo-controlled study with subcutaneous recombinant human erythropoietin in patients with low-risk myelodysplastic syndromes. Br J Haematol 1998; 103: 1070-4
30. Negrin RS, Stein R, Vardiman J, et al. Treatment of the anemia of myelodysplastic syndromes using recombinant human granulocyte colony-stimulating factor in combination with erythropoietin. Blood 1993; 82: 737-43
31. Hellström-Lindberg E, Ahlgren T, Beguin Y, et al. Treatment of anemia in myelodysplastic syndromes with granulocyte colony-stimulating factor plus erythropoietin: results from a randomized phase II study and long-term follow-up of 71 patients. Blood 1998; 92: 68-75
32. Ludwig H, Sundal E, Pecherstorfer M, et al. Recombinant human erythropoietin for the correction of cancer associated anemia with and without concomitant cytotoxic chemotherapy. Cancer 1995; 76: 2319-29
33. Mittelman M, Neumann D, Peled A, et al. Erythropoietin induces tumor regression and antitumor immune responses in murine myeloma models. Proc Natl Acad Sci U S A 2001; 98: 5181-6
34. Del Mastro L, Venturini M, Lionetto R, et al. Randomized phase III trial evaluating the role of erythropoietin in the prevention of chemotherapy-induced anemia. J Clin Oncol 1997; 15: 2715-21
35. Seidenfeld J, Piper M, Flamm C, et al. Epoetin treatment of anemia associated with cancer therapy: a systematic review and meta-analysis of controlled clinical trials. J Natl Cancer Inst 2001; 93: 1204-14
36. Thews O, Kelleher DK, Vaupel P. Erythropoietin restores the anemia-induced reduction in cyclophosphamide cytotoxicity in rat tumors. Cancer Res 2001; 61: 1358-61
37. Lee WR, Berkey B, Marcial V, et al. Anemia is associated with decreased survival and increased locoregional failure in patients with locally advanced head and neck carcinoma: a secondary analysis of RTOG 85-27. Int J Radiat Oncol Biol Phys 1998; 42: 1069-75
38. Fein DA, Lee WR, Hanlon AL, et al. Pretreatment hemoglobin level influences local control and survival of T1-T2 squamous cell carcinomas of the glottic larynx. J Clin Oncol 1995; 13: 2077-83
39. Dubray B, Mosseri V, Brunin F, et al. Anemia is associated with lower local-regional control and survival after radiation therapy for head and neck cancer: a prospective study. Radiology 1996; 201: 553-8
40. Dische S. Radiotherapy and anaemia—the clinical experience. Radiother Oncol 1991; 20 Suppl. 1: 35-40
41. Shasha D. The negative impact of anemia on radiotherapy and chemoradiation outcomes. Semin Hematol 2001; 38 (3 Suppl. 7): 8-15
42. Kelleher DK, Matthiensen U, Thews O, et al. Tumor oxygenation in anemic rats: effects of erythropoietin treatment versus red blood cell transfusion. Acta Oncol 1995; 34: 379-84
43. Kelleher DK, Matthiensen U, Thews O, et al. Blood flow, oxygenation, and bioenergetic status of tumors after erythropoietin treatment in normal and anemic rats. Cancer Res 1996; 56: 4728-34
44. Thews O, Koenig R, Kelleher DK, et al. Enhanced radiosensitivity in experimental tumours following erythropoietin treatment of chemotherapy-induced anaemia. Br J Cancer 1998; 78: 752-6
45. Stüben G, Thews O, Pöttgen C, et al. Recombinant human erythropoietin increases the radiosensitivity of xenografted human tumours in anaemic nude mice. J Cancer Res Clin Oncol 2001; 127: 346-50
46. Bush RS. The significance of anemia in clinical radiation therapy. Int J Radiat Oncol Biol Phys 1986; 12: 2047-50
47. Fyles AW, Milosevic M, Pintilie M, et al. Anemia, hypoxia and transfusion in patients with cervix cancer: a review. Radiother Oncol 2000; 57: 13-9
48. Sweeney PJ, Nicolae D, Ignacio L, et al. Effect of subcutaneous recombinant human erythropoietin in cancer patients receiving radiotherapy: final report of a randomized, open-labelled, phase II trial. Br J Cancer 1998; 77: 1996-2002
49. Lavey RS, Dempsey WH. Erythropoietin increases hemoglobin in cancer patients during radiation therapy. Int J Radiat Oncol Biol Phys 1993; 27: 1147-52
50. Henke M, Guttenberger R, Barke A, et al. Erythropoietin for patients undergoing radiotherapy: a pilot study. Radiother Oncol 1999; 50: 185-90
51. Glaser CM, Millesi W, Kornek GV, et al. Impact of hemoglobin level and use of recombinant erythropoietin on efficacy of preoperative chemoradiation therapy for squamous cell carcinoma of the oral cavity and oropharynx. Int J Radiat Oncol Biol Phys 2001; 50: 705-15
52. Groopman JE, Itri LM. Chemotherapy-induced anemia in adults: incidence and treatment. J Natl Cancer Inst 1999; 91: 1616-34
53. Ray-Coquard I, Le Cesne A, Rubio MT, et al. Risk model for severe anemia requiring red blood cell transfusion after cytotoxic conventional chemotherapy regimens. The Elypse 1 Study Group. J Clin Oncol 1999; 17: 2840-6
54. Skillings JR, Sridhar FG, Wong C, et al. The frequency of red cell transfusion for anemia in patients receiving chemotherapy. A retrospective cohort study. Am J Clin Oncol 1993; 16: 22-5
55. Hellström-Lindberg E, Negrin R, Stein R, et al. Erythroid response to treatment with G-CSF plus erythropoietin for the anaemia of patients with myelodysplastic syndromes: proposal for a predictive model. Br J Haematol 1997; 99: 344-51
56. Ludwig H, Fritz E, Leitgeb C, et al. Prediction of response to erythropoietin treatment in chronic anemia of cancer. Blood 1994; 84: 1056-63

57. Henry D, Abels R, Larholt K. Prediction of response to recombinant human erythropoietin (r-HuEPO/epoetin-alpha) therapy in cancer patients. Blood 1995; 85: 1676-8
58. 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
59. Hellström-Lindberg E. Efficacy of erythropoietin in the myelodysplastic syndromes: a meta-analysis of 205 patients from 17 studies. Br J Haematol 1995; 89: 67-71
60. Ortega A, Dranitsaris G, Puodziunas AL. What are cancer patients willing to pay for prophylactic epoetin alfa?. A cost-benefit analysis. Cancer 1998; 83: 2588-96
61. Cremieux PY, Finkelstein SN, Berndt ER, et al. Cost effectiveness, quality-adjusted life-years and supportive care. Recombinant human erythropoietin as a treatment of cancer-associated anaemia. Pharmacoeconomics 1999; 16: 459-72
62. Sheffield R, Sullivan SD, Saltiel E, et al. Cost comparison of recombinant human erythropoietin and blood transfusion in cancer chemotherapy-induced anemia. Ann Pharmacother 1997; 31: 15-22
63. Barosi G, Marchetti M, Liberato NL. Cost-effectiveness of recombinant human erythropoietin in the prevention of chemotherapy-induced anaemia. Br J Cancer 1998; 78: 781-7
64. Meadowcroft AM, Gilbert CJ, Maravich-May D, et al. Cost of managing anemia with and without prophylactic epoetin alfa therapy in breast cancer patients receiving combination chemotherapy. Am J Health Syst Pharm 1998; 55: 1898-902
65. Kavanagh BD, Fischer BA, Segreti EM, et al. Cost analysis of erythropoietin versus blood transfusions for cervical cancer patients receiving chemoradiotherapy. Int J Radiat Oncol Biol Phys 2001; 51: 435-41
66. Negrin RS, Stein R, Doherty K, et al. Maintenance treatment of the anemia of myelodysplastic syndromes with recombinant human granulocyte colony-stimulating factor and erythropoietin: evidence for in vivo synergy. Blood 1996; 87: 4076-81
67. Griggs JJ, Mushlin AI. Economic analysis of expensive technologies: the case of erythropoietin. Cancer 1998; 83: 2427-9
68. Brandberg Y. Quality of life in clinical trials: assessment and utility with special reference to rHuEPO. Med Oncol 1998; 15 Suppl. 1: 8-12

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