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A Risk-Benefit Assessment of Epoetin in the Management of Anaemia Associated with Cancer

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Abstract

Many patients with solid tumours or haematological malignancies develop anaemia, and the use of chemotherapy aggravates this condition. Red blood cell transfusions are often necessary but are associated with many risks, including immunosuppressive effects that may increase the risk of tumour recurrence.

Many clinical studies have shown that epoetin (recombinant human erythropoietin) therapy can ameliorate, or even prevent, the anaemia associated with chemotherapy and cancer (including solid tumours as well as multiple myeloma or lymphoma). Response, defined as a significant (>50%) reduction in the rate of transfusions and/or a significant (>2 g/dl) elevation of haemoglobin levels, is usually observed in about 60% of the patients, irrespective of the type of standard chemotherapy given. The decrease in transfusion requirements is the major objective of epoetin therapy, because they are costly, inconvenient and are associated with potential adverse effects.

Epoetin therapy also brings about substantial improvements in various indices of quality of life that are proportional to changes in haemoglobin level. However, large dosages of epoetin are generally required and about 40% of patients do not respond even to very high dosages.

A number of adverse effects of epoetin therapy have been observed in patients with renal failure. The most prominent include hypertension, headaches, seizures

and thrombotic events. These complications can also occur in patients with renal failure who are not receiving epoetin. Their exact incidence has been assessed in placebo-controlled studies, which have demonstrated that there is no increased risk of thrombosis or seizure with epoetin. However, it is now generally accepted that 10 to 20% of haemodialysis patients will experience an elevation of blood pressure because of epoetin and there is no doubt that a rapid elevation of blood pressure may cause generalised seizures.

In other settings, including anaemia associated with cancer, very few adverse effects have been attributed to epoetin. However, close monitoring of blood pressure should be implemented in patients with hypertension. There is no evidence that epoetin stimulates tumour growth. With the dosages of epoetin currently used, there is no evidence of stem cell competition, resulting in thrombocytopenia or neutropenia, or of stem cell exhaustion, producing secondary anaemia when treatment is stopped. Epoetin is a remarkably well tolerated drug that offers significant benefits in patients with cancer.

Many patients with cancer, including those with solid tumours or haematological malignancies, develop anaemia that can be further worsened by the use of chemotherapy. Clinical studies have shown that epoetin (recombinant human erythropoietin) therapy can ameliorate or even prevent the anaemia associated with cancer and chemotherapy, reduce the need for transfusions and improve quality of life (QOL). A decrease in transfusion requirements is the major objective of epoetin therapy, reducing the cost, inconvenience and potential adverse effects of blood transfusions. However, large dosages are generally required and many patients do not respond even to very high dosages of epoetin.

A number of adverse effects of epoetin therapy have been observed in patients with renal failure, in particular hypertension, headaches, seizures and thrombotic events. Because these complications also occur in patients with renal failure not receiving epoetin, their exact incidence has been assessed in placebo-controlled studies. These have demonstrated that there is no increased risk of thrombosis, seizures or other adverse effects, except hypertension and headaches, with epoetin. Therefore, in this article we critically review the safety profile of epoetin in renal failure and other indications, based on placebo-controlled studies. We then discuss the results of prospective randomised trials of epoetin therapy in patients with cancer that have been published in peer-reviewed journals. A few other papers have also been included if they provide specific information not available in the prospective trials. Treatment in patients with a myelodysplastic syndrome following haemopoietic stem cell transplantation is not discussed because this particular setting is quite different from that of anaemia associated with cancer in general.

1. Treatment of Anaemia Associated with Cancer

1.1 Treatment Options

Based on our knowledge of the pathophysiology of anaemia associated with cancer, it is clear that the most useful approach is to treat the underlying malignant disorder.[1,2] However, red blood cell transfusions are commonly given to patients with cancer[3] and the transfusion rate is highly dependent on the type of cancer and baseline haemoglobin level.[4] Aberrations, including transfusion reactions, positive antibody screening necessitating further investigation, and clinically significant antibodies requiring antigen-negative units, occurred in 22% of 219 cancer patients needing transfusions.[5] There is controversy about who should receive red blood cell transfusions and who should not. Prudent strategies for elective red blood cell transfusion have been reviewed.[6] Whereas most

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clinicians would transfuse patients with a haemoglobin level of <8 g/dl and aregenerative anaemia, differences in clinical judgement make it difficult to make definite recommendations for patients with haemoglobin levels between 8 and 10 g/dl.[7]

Therefore, alternative patterns of care should be proposed for the management of cancer anaemia. A wide range of options exist for surgery, of which the most useful strategy would be to avoid transfusions altogether by maintaining blood volume with colloid preparations, by using scrupulous surgical techniques and by giving pharmacological agents, such as desmopressin, that are capable of reducing blood losses.[7] The transfusion of autologous red blood cells may take several forms including preoperative autologous blood deposit, perioperative haemodilution, and intra- or postoperative blood salvage.[7] In this context, epoetin may be of particular value in increasing the number of autologous units collected before surgery, as well as in stimulating endogenous erythropoiesis, thereby accelerating recovery from postoperative anaemia.[8,9] Epoetin is now routinely used for the treatment of anaemia associated with renal failure and has been widely tested in the treatment of cancer anaemia in patients receiving or not receiving concomitant chemotherapy.[1,10-12]

1.2 Adverse Effects of Transfusions

Most of the reluctance for blood transfusions stems from the known associated risks.[7,13] Elderly patients may develop pulmonary oedema as a result of fluid overload. The single biggest cause of mortality remains transfusion of incompatible blood resulting from mislabelling of the blood or confusion of 2 patients at the time of transfusion.[7] This causes acute intravascular haemolysis. Other noninfectious complications of blood transfusion include delayed haemolytic reactions, febrile nonhaemolytic reaction to donor white blood cells, allergic reactions to donor proteins, transfusion-related acute lung injury and transfusion-associated graft-versus-host disease.[14] The cellular immune system, antigen-antibody interactions and cytokines all play a role in the pathophysiology of these reactions.[14] Another complication of transfusion is the development of alloimmunisation to red blood cell and platelet antigens,[13] resulting in problems obtaining compatible blood and in refractoriness to platelet transfusions. Progressive iron overload is an inevitable consequence of multiple red blood cell transfusions, and iron toxicity causes heart, liver and multiple endocrine abnormalities.[15] The risk of transmission of infection, including bacterial infection,[16] cytomegalovirus (CMV) infection,[17] hepatitis B or C infection,[18] and HIV or other retrovirus infection[19] has been of major concern. Donor selection to exclude high-risk individuals, combined with serological screening test, has dramatically reduced the risks of HIV, hepatitis B and hepatitis C transmission by blood transfusion, but these risks are still there.

Of particular concern for patients with cancer are the immunomodulatory effects of transfusion.[7,20-22] Although transfusions appear to increase the generation of host suppressive activity, the mechanism of immune modulation remains poorly characterised.[20,21] Whereas this immunomodulatory effect of allogeneic blood transfusion is beneficial for renal allograft recipients and patients with some other selected conditions, this could also be associated with an increased incidence of postoperative bacterial infections and stimulation of tumour growth.[20,21] Most of the available clinical data are from analyses examining the effect of perioperative allogeneic blood transfusions on the recurrence rate and/or survival after surgical treatment of colorectal carcinoma.

Two groups have carried out meta-analyses. Results of the first analysis showed that the cumulative odds ratios for colorectal carcinoma recurrence, cancer-associated death and death from any cause in patients transfused with allogeneic blood products were 1.80, 1.76 and 1.63, respectively.[23] The second analysis showed that allogeneic blood transfusions were associated with a deleterious effect which increased the risk of cancer recurrence by 37% (relative risk 1.37; 95% confidence interval 1.20 to 1.56).[22] Although the authors of this second analysis stated that this 37% increase was

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marginal and could be explained by confounding variables that had not been accounted for, they were unable to rule out a true effect of allogeneic blood itself. Studies showing a significant transfusion effect tended to involve more patients and more multivariate analyses.[21] It is also noteworthy that among 27 retrospective or prospective, but nonrandomised, studies involving about 10 000 patients, 16 found a deleterious effect of transfusions, 11 detected no influence of transfusions, and only one showed benefit from transfusions, which is hardly compatible with a pure chance finding.

The use of autologous blood could theoretically reduce the risk of cancer recurrence. A recent randomised trial compared the prognosis of patients with colorectal cancer receiving autologous or allogeneic blood at the time of surgery, and found no difference in recurrence rates or cancer-specific survival rates between the 2 groups.[24] However, compared with untransfused patients, autologous as well as allogeneic transfusions were associated with a poor prognosis, probably because of the circumstances that made transfusions necessary.[25] Blood transfusions are more likely to be associated with tumours with unfavourable characteristics, and to be given to patients with other clinical conditions that may adversely impact on survival without increasing the risk of tumour recurrence.[26] Indeed, in some studies the association of increased risk of tumour recurrence and allogeneic blood existed for local tumour recurrence but not for distant metastases.[27,28] In contrast, another study of 120 patients with potentially curable and resectable colorectal cancer, randomised to receive either allogeneic or autologous blood, concluded that transfusion of allogeneic blood was an independent adverse prognostic factor for recurrence rate.[29] Because 33% of patients allocated to autologous blood required additional allogeneic blood, this conclusion was not based on an intention-to-treat analysis but on an on-treatment multivariate analysis.

The deleterious effects of allogeneic blood on cancer prognosis have been attributed to donor-derived white blood cells. Animal studies have shown that these adverse effects on recipients with established tumours could be greatly reduced by pre-storage, but not post-storage, leucodepletion.[30] Compared with transfusions of packed red blood cells, transfusions of whole blood adversely affected disease-specific survival after curative resection of colorectal carcinoma.[26] However, a controlled randomised trial comparing leucocyte-depleted blood cells or packed cells without buffy coat in 697 patients with colorectal cancer showed no difference in survival, disease-free survival, cancer recurrence rate or overall infection rate showed no difference between these two types of blood.[31] Nevertheless, patients who received blood of any sort had a lower survival and a higher infection rate than untransfused patients, but a similar cancer recurrence rate.

To ensure homogeneity for all confounding variables between treatment arms, it is important to analyse data on an intention-to-treat basis. Based on this principle, a meta-analysis of randomised, controlled trials comparing buffy coat–depleted allogeneic red blood cells with autologous or leucocyte-depleted red blood cells detected no association between type of blood transfused and cancer recurrence, death due to cancer, or postoperative bacterial infection.[32] However, more than 50% of the patients were not treated according to intention because a large number of 'drop-outs' (patients who did not receive a transfusion), 'drop-ins' (patients who received allogeneic transfusions who were allocated to autologous blood), and also because of random assignment of ineligible patients (non-neoplastic disease or advanced disease at surgery), which blurred the picture considerably.

The influence of allogeneic blood on relapse rate and survival has also been investigated in a variety of other malignancies, including breast, lung, prostate, stomach, kidney, head and neck, cervix, vulva, bone and soft tissue cancer. Approximately two-thirds of these studies reported an adverse effect of allogeneic blood, with the remaining ones showing no effect.[7,20] A prospective cohort study of 37 337 cancer-free women 55- to 69-years-old showed that previous blood transfusion

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may be a risk factor for non-Hodgkin's lymphoma and kidney cancer, but not for the most common neoplasms such as breast, lung, ovary or colon cancer, or for all cancers considered together.[33] Prospective, randomised studies are thus still most needed in this area.

1.3 Epoetin Therapy for Anaemia Associated with Cancer

A large multicentre, double-blind, placebo-controlled trial has assessed the clinical utility of epoetin in patients with anaemia and advanced cancer.[34-36] Three groups of patients were considered. Patients not receiving concomitant chemotherapy (n = 124) were randomised to receive either epoetin 100 U/kg or placebo by subcutaneous injection 3 times a week for 8 weeks. Patients receiving chemotherapy with (n = 132) or without (n = 157) cisplatin received epoetin 150 U/kg or placebo by subcutaneous injection 3 times weekly for 12 weeks. Approximately two-thirds of the patients had solid tumours and one-third had haematological malignancies excluding primary myeloid malignancy or acute leukaemia. Baseline haematocrit was <32%, and 50% of the patients had received transfusions in the 2 to 3 months prior to entry into the study.

From baseline to last value, the haematocrit of epoetin-treated patients increased by a significantly greater amount than the haematocrit in placebo-treated patients: +2.9% in the non-chemotherapy group, +5.8% in the chemotherapy group and +4.7% in the cisplatin group. For epoetin recipients, response (haematocrit increase ≥6%) and complete response (haematocrit ≥38%) rates were 32 and 21% in the non-chemotherapy group, 58 and 40% in the chemotherapy group, and 48 and 36% in the cisplatin group, respectively. Whereas there was no significant difference in the rate of transfusions between placebo and epoetin during the first month, the difference became highly significant during the second and third months in the chemotherapy and cisplatin groups: 28% of patients receiving epoetin required transfusion *vs* 46% of patients receiving placebo. Because of the relatively low dosages of epoetin and the short duration of treatment there was no difference in the rate of transfusion during the second month in the non-chemotherapy group. The response rate was similar in patients with or without bone marrow infiltration by the tumour, as well as in patients with all categories of haematological malignancies and solid tumours.

The changes in QOL parameters were statistically significant in patients who responded to treatment. The incidence of adverse events was not different in patients receiving epoetin or placebo, except for shortness of breath, which was reported more frequently in patients receiving placebo. Overall, there was no difference in neutrophil and platelet counts and the dosage of chemotherapy administered was similar in epoetin or placebo-treated patients.[34,36,37]

In a survey of 2030 patients with haematological (23%) and nonhaematological (77%) tumours receiving platinum (n = 796) or nonplatinum (n = 1224) chemotherapy, treatment with subcutaneous epoetin was started at a dosage of 150 U/kg 3 times a week and increased to 300 U/kg 3 times a week after 8 weeks if necessary.[38] Whereas 37% of the patients required transfusions before the study, only 10% needed them by the third month of the study and 58% became transfusion-independent after the first month. However, 18% of those who were transfusion-independent at baseline needed transfusions in the first month on study. Self-rated scores for energy level, activity level and overall QOL improved significantly with therapy, and changes in QOL correlated with changes in haemoglobin level. Improvements in QOL and haemoglobin level were important in patients entering complete or partial remission of their underlying disease and negligible in those with progressive disease (only noticeable in the few patients showing a haemoglobin level increase >4 g/dl). Despite similar increases in haemoglobin level, changes in QOL were less prominent in patients with no response or stable disease compared with those experiencing remission. Similar improvement in QOL was also noted in another smaller

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study,[39] but the results of large, randomised, placebo-controlled studies are awaited to definitively confirm these important and very promising observations.

1.4 Epoetin Therapy for Patients with Multiple Myeloma or Malignant Lymphoma

Rose et al.,[40] in a randomised, double-blind, placebo-controlled trial that has only been published in abstract form, investigated the effect of subcutaneous epoetin 150 U/kg 3 times per week in 221 patients with anaemia and chronic lymphocytic leukaemia. After 3 months, haematocrit increased by 5.7% in the epoetin group *vs* 1.5% in the placebo group. In addition, 50 *vs* 15% had a change ≥6% from baseline, and 30 *vs* 5% achieved a haematocrit of ≥38%. Patients whose haematocrit reached 38% showed significant improvements in energy, self-rated health, physical function, emotional function, social function and mental health.

Cazzola and colleagues[41] conducted a randomised, controlled, multicentre study comparing various dosages of epoetin ranging from 1000 to 10 000 U/day. Epoetin was administered subcutaneously for 8 weeks to 146 untransfused patients with multiple myeloma or non-Hodgkin's lymphoma and stable anaemia, of whom 79% received chemotherapy during the study. Except in patients receiving 1000 U/day, there was a dosage-dependent elevation of haemoglobin levels, and the probability of response (haemoglobin increase ≥2 g/dl) ranged from 31% at a dosage of 2000 U/day to around 60% at dosages of 5000 or 10 000 U/day. As approximately 75% of the patients presenting with inappropriately low serum erythropoietin levels responded while only 25% of those with adequate erythropoietin levels did so, a low serum erythropoietin level (≤50 mU/ml) or low observed-to-predicted ratio (≤0.9) were the most important predictive factors of response. As recommended by the authors, the initial dosage should be 2000 U/day if the patient's platelet count is normal (i.e. indicating normal residual marrow function) or 5000 U/day if platelet count is reduced.

In a randomised controlled multicentre study, Osterborg et al.[42] investigated the effect of subcutaneous epoetin on transfusion requirements in transfusion-dependent patients with multiple myeloma or non-Hodgkin's lymphoma. Patients were randomised between no epoetin, a fixed dosage of 10 000 U/day and stepwise escalating dosages from 2000 to 10 000 U/day, all given for 6 months. Of 121 evaluable patients, 91% received chemotherapy during the study. The cumulative response rate, defined as elimination of transfusion and an increase in haemoglobin level of >2 g/dl, was 60% in both epoetin groups versus 24% in the placebo group. This translated into fewer transfusion requirements. Response was delayed in the titration group because only 14% of the patients responded to the first dosage level. Multivariate regression analysis showed that a low baseline serum erythropoietin level or a ratio of observed-to-predicted serum erythropoietin level of <0.9 were the strongest predictors of response. There was no significant difference between multiple myeloma and non-Hodgkin's lymphoma patients.

1.5 Epoetin Therapy for Patients with Solid Tumours

Cascinu and colleagues[43] conducted a double-blind, placebo-controlled, randomised trial in 100 patients with cisplatin-associated anaemia (haemoglobin level <9 g/dl, down from at least 11 g/dl before chemotherapy). All of them received cisplatin with or without etoposide or fluorouracil. The dosage of epoetin was 300 U/kg/week given subcutaneously in 3 injections for 9 weeks. At 3, 6 and 9 weeks of therapy, haemoglobin levels were significantly higher in the epoetin-treated group. At the end of the study, 82% of treated patients had a haemoglobin level of >10 g/dl whereas only 2% of the patients in the placebo arm had a haemoglobin levels that were that high. Only 20% of the patients receiving epoetin required transfusions *vs* 58% in the placebo group.

Porter et al.[44] randomised 24 paediatric patients with solid tumours to receive either placebo or epoetin together with oral iron for 16 weeks. The

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starting dosage of epoetin was 150 U/kg given intravenously or subcutaneously 3 times per week and this dosage was escalated by 50 U/kg increments until transfusion independence or a maximum of 300 U/kg was reached. Almost all patients needed red blood cell transfusions but requirements were cut by 70% in patients receiving epoetin. Platelet transfusions were needed by 40% of control patients versus none of the treated patients. There was no difference in neutrophil counts between the 2 groups, but granulocyte colony-stimulating factor was used in the majority of the patients in both groups.

30 patients with anaemia (haemoglobin level <11 g/dl) undergoing chemotherapy for primary malignant bone tumours were randomised by Wurnig et al.[45] to receive twice weekly intravenous injections of either epoetin 600 U/kg or a placebo for 20 weeks. Although there was no difference in haemoglobin levels at any time, the number of transfusions was significantly decreased in the epoetin group from week 8 of therapy, and the benefits became even more evident with continuation of therapy. The number of red blood cell units transfused was reduced on average by 6 per patient in the treatment group. There was no difference in platelet or white blood cell counts throughout the study.

1.6 Epoetin Therapy for Prevention of Anaemia in Patients with Solid Tumours

Welch and colleagues[46] investigated the ability of epoetin to prevent the development of anaemia in 30 patients with ovarian carcinoma who were scheduled to receive chemotherapy with cisplatin and/or carboplatin. Patients were randomised to receive either epoetin at a dosage of 900 U/kg/week in 3 subcutaneous injections or supportive treatment alone for up to 6 cycles of chemotherapy. A highly significant difference in mean haemoglobin levels between the 2 treatment groups became apparent after cycle 1 of treatment and this difference peaked after cycle 3. The difference was due to a significant decrease in haemoglobin levels in the control arm. Compared with 8 out of 15 control patients, only 4 out of 15 patients in the treatment group required red blood cell transfusions; however, this difference was not significant.

De Campos et al.[47] randomised 36 patients with small-cell lung cancer onto a 3-arm trial comparing no additional treatment with either 150 or 300 U/kg epoetin administered subcutaneously 3 times a week for a maximum of 6 cycles of carboplatin-based chemotherapy. Haemoglobin levels decreased in all patients, but the onset of anaemia was significantly delayed in patients receiving epoetin and the total number of red cell transfusions was decreased by 50% in these patients. No differential effect was noted between the 2 dosages of epoetin. There was also a nonsignificant trend towards higher platelet counts and fewer platelet transfusions in the epoetin group.

2. Adverse Effects of Epoetin Therapy

2.1 Patients with Renal Failure

The adverse events associated with administration of epoetin to patients with renal failure have been well characterised.[48,49] In the early days, a high incidence of hypertension, seizures and thromboembolic complications was reported in uncontrolled studies. Only 2 placebo-controlled studies have been conducted in patients receiving dialysis. The Canadian Erythropoietin Study Group[50] reported that patients receiving epoetin had a significant increase in diastolic blood pressure. However, there was no difference in the incidence of severe hypertension or hypertension-related seizures between placebo-treated patients (13%) and those receiving epoetin (14%). Bennett[49,51] reported an 83% incidence of adverse events in patients receiving haemodialysis treated with epoetin. The most frequently reported events were abdominal pain, chest pain, generalised aches, diarrhoea, nausea, vomiting, insomnia, dyspnoea, hypertension and arteriovenous fistula clotting. However, all these adverse reactions occurred with the same frequency in placebo-treated patients, indicating that they related to the renal failure itself rather than to epoetin therapy. The only

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exception was headache, possibly an indirect sign of intracranial hypertension, which occurred in 15% of epoetin-treated and none of the placebo-treated patients.

There is only 1 placebo-controlled study in predialysis patients.[52] There was no statistically significant difference for changes in either systolic or diastolic blood pressure among patients treated with 50, 100, 150 U/kg epoetin or placebo. However, there was a trend toward an increased number of hypertensive events classified as an adverse experience by the investigator in the patients receiving epoetin 150 U/kg whose haematocrit rose rapidly. The degradation of renal function and the incidence of all other adverse events, including headaches and seizures, were not increased in epoetin-treated patients.

It is now generally accepted that 10 to 20% of patients receiving haemodialysis will experience an elevation of blood pressure because of epoetin treatment.[53] Risk factors for the development or worsening of hypertension may include pre-existing hypertension, the presence of native kidneys, a rapid increase in haematocrit, a low baseline haematocrit, high dosages of epoetin and the intravenous route of administration.[54] The pathophysiology of hypertension could relate to increased blood viscosity, loss of hypoxic vasodilation with consequent increased peripheral resistance, activation of neurohumoral systems, as well as direct vascular effects of the drug, including increased cell calcium uptake, imbalance in local vasoactive agents (increased synthesis of endothelin, shift in the balance of constrictor and relaxant prostanoids), mitogenic effect on smooth muscle cells and enhanced platelet reactivity.[48,54,55]

Seizures associated with epoetin therapy appear to be a form of hypertensive encephalopathy, but their incidence is similar in placebo-treated patients as well as in a series of untreated dialysis patients.[55] However, there is no doubt that a rapid elevation of blood pressure following epoetin therapy may cause generalised seizures, and blood pressure should thus be assessed prospectively in these patients.

Although epoetin therapy usually produces an increase in blood viscosity and an improvement in the haemostatic defect of uraemia requiring a 10 to 20% increment of the dosage of heparin, the incidence of thromboembolic events is not changed compared with placebo.[48,53,56] The higher oxygen transport capacity due to elevated haematocrit is not offset by decreased tissue perfusion due to increased peripheral resistance, resulting in no more episodes of myocardial, cerebral or peripheral ischaemia.[53]

Finally, flu-like symptoms[48] and pain after subcutaneous injection[56] relate more to the mode of administration and the vehicle used than to epoetin itself.

2.2 Nonrenal Settings

The experience in patients with renal failure emphasises the need to rely on placebo-controlled studies to assess the toxicity of epoetin therapy in other settings as well. Repeated administration of intravenous or subcutaneous injections of epoetin in healthy volunteers was not associated with any more adverse reactions compared with placebo.[57] When either placebo or epoetin therapy was given to patients in combination with repeated phlebotomies, epoetin was not associated with any significant clinical or laboratory adverse effects, even after a detailed analysis of coagulation and blood pressure parameters.[58] The only exception was a significant, though clinically irrelevant, elevation of platelet counts, also encountered in haemodialysis patients.[59] Numerous placebo-controlled studies have demonstrated that epoetin is well tolerated and effective in increasing preoperative deposit of autologous blood, thus reducing the need for exposure to allogeneic blood during surgery.[60-62] Similarly, perioperative epoetin treatment in elective hip replacement was not associated with more thrombotic (screened for by venography or ultrasonography) or other adverse events than placebo.[63] Detailed investigation of haemostasis, fibrinolysis and blood rheology in autologous blood donors treated with epoetin showed no evidence of prothrombotic changes.[64] However, the preopera-

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tive occurrence of thrombotic events in placebo- and epoetin-treated patients suggests that these events may be associated with aggressive autologous blood removal, implying that this practice may be unwise in high-risk cardiac patients.[65]

Combined analysis of 4 randomised, double-blind, placebo-controlled clinical trials in patients with AIDS who were receiving zidovudine therapy showed no difference among placebo- or epoetin-treated patients in the incidence of adverse effects or opportunistic infections.[66] In the anaemia of prematurity, tolerance to epoetin has been excellent with no serious adverse effects attributed to treatment.[67] Although a significant decrease in neutrophil counts has been observed in small uncontrolled studies, this complication has not been encountered in randomised trials. Elevation of blood pressure in nonrenal patients is only marginal and is never associated with malignant hypertension or seizures.

2.3 Patients with Cancer

The largest placebo-controlled study in patients with cancer has been published as 3 sub-trials,[34,36] including patients receiving no chemotherapy, nonplatinum-based chemotherapy[35] or platinum-based chemotherapy. The incidence of adverse events in epoetin-treated patients was not different from the incidence in placebo-treated patients, except for shortness of breath, which was seen twice as frequently in patients receiving placebo. The incidences of thrombotic events, seizures, death, disease progression or treatment discontinuation were also comparable between treatment and placebo groups. Hypertension was noted in 5.2% of epoetin-treated patients and 3.5% of placebo-treated patients, and it was never malignant nor associated with hypertensive encephalopathy. Although the difference was not significant, individual case histories suggested that a rapid rise in haematocrit might be associated with hypertension in a few patients. There was no difference between the placebo and epoetin arms in neutrophil and platelet counts throughout therapy. In the subgroup of patients receiving chemotherapy without cisplatin, an increased occurrence of diarrhoea and diaphoresis was noted with epoetin.[35] As this has never been reported in any other trial of epoetin for any indication, it is probably a chance finding.

In a placebo-controlled study published by Osterborg et al.,[42] the incidence of general and serious adverse effects was 84 and 57%, respectively, in epoetin-treated patients, and 65 and 45% in control patients, respectively. The differences were due to a higher incidence of infectious complications in the epoetin-treated groups. Median neutrophil and platelet counts in all groups did not change during the study. Nonserious hypertension and bone pain were also more frequent in epoetin-treated patients compared with patients in the control group. The rates of tumour progression and death from all causes were similar in treated and control patients, but more patients treated with epoetin died from infection. However, all events leading to death were classified as unrelated to epoetin therapy.

In a placebo-controlled trial conducted by Cazzola et al.,[41] the incidence of serious adverse events (14 *vs* 13%) as well as that of any adverse event of special interest, such as hypertension, angina pectoris, cerebral ischaemia, or malignancy progression, was identical in the epoetin and control groups. The number of deaths was even higher in the control (10.3%) versus the treated (3.4%) groups. No data are available on the evolution of platelet and neutrophil counts.

In the study published by Welch and colleagues in patients with ovarian carcinoma,[46] the incidence of adverse experiences was similar in epoetin-treated and control patients, with more headaches in the treatment arm and more flu-like symptoms and epistaxis in the control arm. Overall, mean systolic and mean diastolic blood pressure decreased throughout the study, although 3 episodes of transient hypertension that occurred in 3 different patients were possibly related to epoetin therapy. One of the patients receiving epoetin developed deep vein thrombosis.

In the trial conducted by Porter et al.,[44] in paediatric patients with solid tumours, toxic effects of

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epoetin were minimal with no cases of hypertension, seizures or thrombosis. In the trials published by Rose et al.,[40] de Campos et al.,[47] Wurnig et al.[45] and Cascinu et al.,[43] there was no particular toxicity reported with epoetin compared with controls, but few details are available.

Finally, a small number of animal studies have pointed to the possible occurrence of a transient exhaustion of erythropoiesis after cessation of intensive stimulation by epoetin,[68] and of potential competition between different cell lineages when one is preferentially and intensively stimulated.[69-72] These preliminary observations remain to be confirmed in other animal, as well as in human, studies. However, even if these animal studies employed high dosages of epoetin, lower dosages may exert similar effects in situations of limited residual haemopoiesis, as may be the case after multiple courses of chemotherapy. This implies that careful consideration should be given before using high dosages of haemopoietic growth factors and that follow-up studies after cessation of treatment with epoetin are warranted in patients with cancer.

2.4 Epoetin and Neoplastic Cell Growth

When treating patients with cancer using epoetin, it is important to make sure that epoetin does not stimulate clonogenic cell proliferation. *In vitro* stimulation of clonogenic cell proliferation was first described in a patient with acute poorly differentiated leukaemia.[73] Two classes of specific erythropoetin receptors were demonstrated at the surface of cells from an erythroleukaemic cell line whose growth was stimulated in the presence of erythropoetin.[74] Antisense oligomers corresponding to erythropoetin or its receptor caused marked suppression of several cell lines of erythroleukaemic cells, suggesting an internal autocrine regulatory mechanism.[75] In another study of leukaemic progenitors obtained from 5 patients with erythroblastic leukaemia, spontaneous autonomous colonies were always obtained.[76] Leukaemic erythroid progenitors from 2 *de novo* leukaemias responded primarily to erythropoietin, whereas those of 3 blast crises of chronic myeloid leukaemia responded maximally to the combination of erythropoietin plus granulocyte-macrophage colony-stimulating factor (GM-CSF). Growth of erythroid colonies derived from the chronic myeloid leukaemia clone is in fact independent of erythropoietin only in the presence of stem cell factor.[77] In another study, epoetin alone had no effect on the growth of clonogenic leukaemic blood cells from 10 patients with acute myeloblastic leukaemia.[78] However, in the presence of phytohaemagglutinin-stimulated lymphocyte conditioned medium (PHA-LCM), leukaemic blast colonies increased with epoetin in 2 of the 10 patients. This effect was observed with GM-CSF or interleukin-3 (IL-3) but not with G-CSF. Kimata and colleagues[79] investigated the effect of epoetin and IL-6 on immunoglobulin production and cell proliferation in 2 human plasma cell lines. Both epoetin and IL-6 induced cell proliferation and enhanced immunoglobulin production by independent mechanisms.

Okuno et al.[80] demonstrated that erythropoietin dosage-dependently stimulated the proliferation of a human myeloma cell line by interacting with saturable specific binding sites. In a similar study, whereas erythropoietin alone did not induce leukaemic colonies, the combination of erythropoietin and PHA-LCM significantly increased the number of leukaemic colonies in 9 out of 12 cases of acute myeloid leukaemia other then erythroleukaemia.[81] Incubation with PHA-LCM induced expression of erythropoietin receptors that were not present on fresh leukaemic blasts. The addition of erythropoietin also increased the self-renewing capacity of leukaemic blasts.

Rosti et al.[82] reported that epoetin did not affect either *in vitro* colony formation or the percentage of cells in S phase in 10 different cell lines derived from both solid tumours and haematological malignancies, including acute myeloblastic leukaemia and erythroleukaemia. Similarly, Berdel et al.[83] observed no significant stimulation of clonal growth in 22 different cell lines derived from a wide range of human solid tumours following exposure to epoetin. In addition, epoetin had no ad-

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ditive effect on those cell lines responsive to IL-3 and GM-CSF. These studies suggest that apart from a few instances in which epoetin stimulated clonogenic growth of erythroleukaemic blasts, there is no independent effect of erythropoietin on tumour cell growth. Epoetin might have some synergistic effect on the growth of myeloblasts when used with GM-CSF or IL-3. However, there is no report that treatment with epoetin can accelerate cancer progression in animals or in humans. Although there are reports in which progression of multiple myeloma[84,85] or occurrence of acute myeloid leukaemia[86] coincided with treatment with epoetin, there was no indication of a causal relationship. In rats bearing an intraperitoneal carcinoma, epoetin caused no enhancement of tumour growth, but rather inhibited tumour growth in non-anaemic animals.[87] There is also the case of a patient with erythroleukaemia in whom it was first confirmed *in vitro* that epoetin could produce differentiation of leukaemic cells.[88] Then subcutaneous epoetin was administered at a dosage of 12 000 U/day to the patient, who was refractory to conventional chemotherapy. A complete remission was obtained which lasted for 3 months, but, following a relapse, the patient's condition did not respond to further treatment.

3. Conclusions

Epoetin is effective in correcting the anaemia, reducing the risk of exposure to allogeneic blood, and improving overall QOL in patients with cancer who are either receiving or are not receiving platinum- or nonplatinum-based chemotherapy. A decrease in transfusion requirements is a major objective of epoetin therapy, thereby reducing the cost, inconvenience and potential adverse effects of blood transfusions, which include a possible risk of increasing the rate of recurrence for specific tumours. However, the immunosuppressive impact of transfusions cannot be considered as proven and other adverse reactions can be minimised by careful transfusion practice. On the other hand, large dosages of epoetin are generally required and many patients do not respond even to these high dosages.

A number of adverse effects of epoetin therapy have been reported in patients with renal failure, including hypertension, headaches, seizures and thrombotic events. Because these complications also occur in patient, with renal failure who are not receiving epoetin, placebo-controlled studies have demonstrated that there was indeed no increased risk of thrombosis or seizures with epoetin. However, 10 to 20% of haemodialysis patients will experience hypertension as a result of epoetin therapy and there is no doubt that a rapid elevation of blood pressure may cause generalised seizures. Very few adverse effects have been conclusively attributed to epoetin in patients with cancer receiving epoetin. However, many studies have excluded patients with a history of hypertension and close monitoring of blood pressure should be implemented in patients with hypertension.

Neither clinical nor *in vitro* studies have shown that epoetin could stimulate tumour growth, except in rare instances of erythroleukaemia. However, induction of differentiation has also been attributed to epoetin in this setting. Animal studies have indicated that high dosages of epoetin may cause stem cell competition, resulting in thrombocytopenia or neutropenia during the course of epoetin therapy, as well as stem cell exhaustion, producing secondary anaemia when treatment is stopped. Fortunately, this has not been a clinical problem so far with the dosages used. Epoetin is a remarkably well tolerated drug that offers significant benefits in patients with cancer.

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