The Handbook

Disorders of iron homeostasis, erythrocytes, erythropoiesis
CHAPTER 8

Treatment of anaemia with erythropoietin

Yves Beguin, Catherine Dujardin, Maude Piron, Gaetan Vanstraelen
1. Introduction
Increased Epo production in response to hypoxia translates into exponential elevation of serum Epo levels (1). Serum Epo levels inappropriately low for the degree of anaemia, indicating blunted Epo production, are encountered not only in chronic kidney disease, but also in a number of other conditions, including the anaemia of chronic disorders (cancer, inflammatory disorders, HIV infection), prematurity, early pregnancy, congestive heart failure and after allogeneic stem cell transplantation (1).

The clinical use of erythropoietin started in 1986 with the treatment of patients with chronic kidney disease. In these subjects, endogenous serum Epo levels are very low and the administration of erythropoietin, restoring adequate levels of the hormone, permits correction of the anaemia. Since then, the indications for the use of erythropoietin therapy to boost erythropoiesis have broadened considerably. Although erythropoietin has become a well-established treatment for many anaemic conditions, in some other clinical situations its use has not been a success.

In the first part of this review, we will discuss clinical experience with erythropoietin therapy for the purpose of stimulating erythropoiesis in patients. Hence, the abuse of erythropoietin for doping purposes in sports (2) or the potential clinical use of the pleiotropic, non-erythropoietic, action of erythropoietin (3, 4) will not be considered here. We will use the term EPO to refer to pharmacological preparations of erythropoietin, including all erythropoietic agents currently available in routine clinical practice (see below), and the term Epo to refer to physiological erythropoietin.

In each clinical indication, we will present almost exclusively the results of phase III randomised trials. When many such trials are available, instead of describing each of them, we will refer to high-quality reviews, meta-analyses and guidelines based on these studies. When few trials have been performed, we will present them individually. When no randomised study covers certain important areas, selected phase II trials will be mentioned. In the second part of the paper, we will focus on topics that are relevant across clinical disorders, including side effects, response modifiers and functional iron deficiency. Emphasis will be placed on more recent data not yet described in available reviews.

2. Erythropoietic agents
With the exception of pure red cell aplasia (see below), there is no known difference in the efficacy and safety profile of Epoetin-α (Janssen-Cilag) and Epoetin-β (Roche) (5), the 2 available brands of recombinant human erythropoietin (rHuEPO). The more convenient SC route ensures more favorable pharmacokinetics and
substantially (~30%) reduces dose requirements (6). Early trials administered rhEPO daily or thrice weekly (TIW), but studies in cancer patients (7) as well as other indications have demonstrated similar efficacy for the same total dose given once weekly or TIW. The useful dose range varies considerably in different clinical disorders, from around 100 U/kg/wk rhEPO in haemodialysis patients to around 1,000 U/kg/wk rhEPO in myelodysplastic syndromes.

Novel long-acting EPO molecules may also considerably prolong exposure to the active drug. Amgen, Inc has produced darbepoetin-α, which differs from rhEPO in containing two additional N-glycosylation sites, resulting from amino acid substitutions in the erythropoietin peptide backbone. The additional carbohydrate content of the molecule prolongs half-life 3-fold (8). The standard schedule of darbepoetin-α is once weekly, but administration every 2-3-4 weeks has been successful (9, 10). A recent study in cancer patients has shown that 40,000 U/wk rhEPO and 200 µg/wk darbepoetin-α achieve similar responses (11). Other data as well point to a 1:200 conversion factor between darbepoetin-α and rhEPO. Another long-acting EPO molecule, named “Continuous Erythropoietin Receptor Activator” (CERA), produced by Roche, is characterised by less tight binding to, and different uptake by, the Epo receptor, resulting in extended half-life. CERA is currently being tested in clinical trials using a dosage schedule of once every 3-4 wks.

Expansion of the erythropoietic marrow in response to EPO is very gradual and it takes several weeks for maximum activity to be achieved (12). Hence, transfusion-independence is rarely achievable before the 2nd and 3rd months of treatment (13). EPO has also been used for the purpose of preventing anaemia or supporting phlebotomy. Therefore, it is impossible to propose uniform response criteria. These criteria must necessarily be partly different when EPO is used for the prevention or the treatment of anaemia. Prevention means that EPO is used in a non-anaemic patient to avert the occurrence of anaemia after certain therapeutic interventions. Treatment signifies that EPO is given to reverse an anaemia that is already present. When treating anaemia, a haemoglobin (Hb) response is often defined by a Hb increase of at least 2 g/dL (or haematocrit (Hct) increase of at least 6%) without transfusion. However, when the entry Hb is 10-11 g/dL and the target Hb 12-13 g/dL, such Hb response may not be achievable before reaching the target Hb. Therefore, haematopoietic response can be defined as either a Ht response of at least 2 g/dL or a Hb increase to >12 g/dL without transfusion. When EPO is given to a transfusion-dependent patient, response could be the achievement of transfusion independence.
CHAPTER 8 • Treatment of anaemia with erythropoietin

3. Clinical applications (Table 1)

Table 1: Potential indications for EPO therapy

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<td>Autologous blood donation</td>
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RA = rheumatoid arthritis, IBD = inflammatory bowel disease, MDS = myelodysplastic syndrome, HIV = human immunodeficiency virus, HC = hepatitis C.

3.1 Chronic kidney disease (CKD)

Anaemia of CKD is the prototype of Epo-deficient state and more than 95% of CKD patients will respond appropriately. The use of EPO therapy for treatment of CKD anaemia can be therefore regarded as the gold standard of EPO therapy (14). Meta-analyses clearly show that EPO therapy increases Hb levels, improves quality of life, almost completely abrogates transfusion needs, reduces the need for hospitalization and improves survival (15). EPO therapy in CKD patients is now universally accepted and practice guidelines have been developed by the European Dialysis and Transplantation Association (European Best Practice Guidelines (EBPG) updated in 2004) (16), and by the National Kidney Foundation (NKF-K/DOQI) (17).

EPO therapy should be initiated when the Hb is below 11 g/dL, irrespective of the need for dialysis. The initial dose for rHuEPO should be 80–120 U/kg/wk (typically 6000 U/wk) if rHuEPO is given SC, or 120–180 U/kg/wk (typically 9000 U/wk) if it is given IV. The SC route thus substantially reduces dose requirements, but Epoetin-α should only be given IV due to the risk of pure red cell aplasia (PRCA). When given IV Epoetin-α should be given 3 times per week. The same would apply to Epoetin-β, but there is no need to use the IV route. The recommended starting dose of darbepoetin-α is 0.45 mg/kg/wk by either IV or SC route (18). Epoetin-β can be given SC once per week and darbepoetin-α can be given SC once every 2 weeks or even less often in the maintenance phase.

The rate of increase in Hb level should be 1–2 g/dL/month; otherwise the dose should be adjusted. Hb concentrations should be determined from samples taken prior to the dialysis session because post-dialysis values are significantly higher (19). The target Hb should be >11 g/dL, which should be reached within four months of therapy. The exact target Hb should be defined for individual patients, taking activity and
co-morbid conditions into account. For example, patients with chronic hypoxemic pulmonary disease may benefit from higher values, whereas Hb levels >12 g/dL are not recommended with severe cardiovascular disease unless symptoms dictate otherwise. Indeed, Hb >13 g/dL in CKD patients with cardiovascular disease is associated with higher all-cause mortality (20). Although dialysis patients without cardiac disease may enjoy an enhanced quality of life with normal Hb levels, this cannot be recommended because minimal data are available to assess the risk of serious cardiovascular events (20-22). In addition, early initiation of EPO therapy in predialysis patients (patients with CKD who do not yet require dialysis) slows the progression of renal anaemia (23) and creatinine clearance may be improved by maintaining high versus low Hb targets (20). Sufficient iron should be administered to all patients. At a minimum, serum ferritin should be >100 mg/L, hypocromic red cells (HYPO) <10%, transferrin saturation (TSAT) >20% and reticulocyte haemoglobin content (CHR) >29 pg. In practice, it is necessary to aim for serum ferritin 200-500 mg/L, HYPO <2.5%, TSAT 30-40% and CHR around 35 pg. Iron should be administered IV at 25-150 mg/wk for the first 6 months of therapy at least, although the optimal frequency of administration is unknown. Between 5 and 10% of patients fail to show a satisfactory response despite high doses of EPO. The definition of hyporesponsiveness is generally regarded as a failure to achieve Hb values 10-11 g/dL despite EPO doses in excess of 200 U/kg/wk (24). Multiple causes of hyporesponsiveness have been identified but the most important ones are iron deficiency, infection or inflammation, and inadequate dialysis (17, 24). The role of adjuvant therapy in improving response, particularly in poor responders, remains controversial. The most provocative data indicate that androgens may improve the efficacy of low-dose EPO therapy (25) or when used alone, may improve the anaemia of male peritoneal dialysis patients in a similar manner to what is observed with EPO therapy (26).

### 3.2 Cancer

Many individual randomised studies have shown that EPO therapy, using rHuEPO-α or -β or using darbepoetin-α, can ameliorate the anaemia associated with cancer and chemotherapy and reduce the need for transfusions by about one third. With an estimated risk of 50% for transfusion, the number of patients needed to treat (NNT) to spare one patient from transfusion is approximately 6, but in a hypothetical population with an estimated risk of 70% for transfusion the NNT is only four (27, 28). From the experience with rHuEPO (29) or darbepoetin-α (30), one can expect approximately 60-70% of cancer patients to respond to EPO therapy by increasing their Hb by at least 2 g/dL (Hb response) or raising their Hb above 12 g/dL (Hb correction).
The type of tumor, in particular haematological versus non-haematological, is not critical, and patients undergoing platinum-based or non-platinum chemotherapy respond similarly. In addition, large community trials (13, 31) as well as meta-analyses (32) have shown that EPO therapy improves quality of life in patients with cancer, particularly when the Hb increases into the 12-13 g/dL range (29). Two groups, the Blue Cross and Blue Shield Association-Technology Evaluation Center (BCBSA-TEC) and the Cochrane Review Group (CRG) have conducted meticulous reviews of existing evidence on the role of EPO in anaemia associated with cancer (27, 28, 33, 34). Based on these reviews, evidence-based clinical practice guidelines have been developed by the American Society of Clinical Oncology and the American Society of Hematology (ASCO/ASH) (35) and by the European Organisation for Research and Treatment of Cancer (EORTC) (36). The more recent EORTC guidelines state that treatment with EPO should be initiated at a Hb level of 9-11 g/dL, depending on anaemia-related symptoms, and that the target Hb concentration should be 12-13 g/dL with the double goal of improving QOL and preventing transfusions. This should be achieved with a total weekly dose of 500 U/kg/wk for rHuEPO or 2.25 µg/kg/wk for darbepoetin-α. There is no evidence that doubling the dose is effective if there has been no response after one month, and this cannot be recommended. After reaching the target Hb, the EPO dose should be reduced and titrated on an individual basis to find the lowest effective dosage. The prophylactic use of EPO therapy in non-anaemic patients is not recommended and may even be deleterious (37, 38). Although none of the published guidelines found good quality data in the literature for a positive effect of iron supplementation, a more recent clinical trial demonstrated that IV iron supplementation boosted response to EPO in patients with evidence of functional iron deficiency, whereas oral iron was not effective (39).

3.3 Myelodysplastic syndrome

The response rate to EPO therapy is much lower in MDS patients than in patients with other forms of cancer (40). These patients may be treated with EPO alone or in combination with low-dose G-CSF, but no study has compared the two approaches. EPO given as monotherapy improves MDS anaemia in approximately 20-25% of patients (40). The only placebo-controlled randomised study of EPO therapy in patients with MDS showed a significant effect of EPO on anaemia and transfusion requirements in the treated group (41). There was no effect in patients who were transfusion-dependent at entry to the study or in patients with RARS. Longer duration of treatment of at least 6 months increased the response rate to 45% (42). When G-CSF is added to EPO, response rates of around 40-60% can be achieved and
G-CSF may induce responses in EPO-resistant patients (40). There is only one randomised trial of EPO + G-CSF (group A) versus supportive care (group B) in patients with low-grade MDS and serum EPO levels <500 U/L (43). Responses were achieved in 10/24 patients in group A versus 0/26 in group B, but were lost in 6/8 patients discontinuing G-CSF and restored after G-CSF was resumed. No effect on quality of life was demonstrated. A meta-analysis of 205 patients treated with EPO alone identified RAS vs. other types of MDS, transfusion-dependence vs. no need for transfusion, and serum Epo levels above 200 U/L vs. lower levels, as predictors of poor response to EPO (44). A predictive model based on serum Epo levels and transfusion requirements (45), and later validated in other series of patients (46, 47), has been proposed for patients treated with EPO + G-CSF. Hence, MDS patients can be treated with EPO alone when they have RA or RAEB with serum Epo <200 U/L and no transfusion need, or with a combination of EPO and G-CSF if they have RA, RAS or RAEB with serum Epo <500 U/L and transfusion needs lower than 2 U/month (40).

3.4 Haematopoietic stem cell transplantation (HSCT)
Three randomised studies (48-50) have looked at the effect of EPO on the time to transfusion independence in patients with haematological malignancies undergoing autologous bone marrow transplantation (BMT). All administered IV rhEPO at doses ranging from 600 to 1400 U/kg/wk for 3-7 weeks and none obtained a decrease in time to transfusion independence or in the number of RBC units transfused. Early randomised trials after allogeneic BMT (allo-BMT) (51-53), administering large IV rhEPO doses ranging from 900 to 3500 U/kg/wk sometimes (51-53), but not always (54), showed some reduction in RBC transfusions. In the largest study, a placebo-controlled multicentre trial in autologous and allogeneic BMT recipients, rhEPO 1050 U/kg/wk was given by continuous IV infusion until day 41 or transfusion independence (55). In auto-BMT patients, there was no effect on erythroid regeneration or RBC transfusions. In allo-BMT recipients, transfusion independence was accelerated but the number of RBC transfusions was not different.

Treating patients with huge (and costly) doses of EPO at a time when the erythroid marrow has not developed enough for erythroid precursors to respond, when endogenous Epo levels are elevated and when many complications may blunt response may not be the best way to use EPO after HSCT. A more physiological alternative could be EPO administration starting one month after transplantation. Indeed, recent phase II trials, in which rhEPO 500 U/kg/wk was started around day 30 post-autologous (56) or allogeneic (57, 58) HSCT was associated with remarkable response and abolishment of transfusion needs. In addition, EPO therapy before high-dose chemotherapy appears an effective strategy for facilitating autologous transplantation without RBC transfusions (59).
3.5 Viral infections (HIV, HC)

The use of EPO therapy in HIV infection has shown that recovery from anaemia was significantly associated with a reduced risk of death (60). Two randomised, placebo-controlled, studies have been conducted in patients with AIDS (61, 62). In these studies, patients with low baseline endogenous Epo (1500 U/L) enjoyed better Hb responses and required fewer transfusions. However, in patients with high baseline endogenous EPO, no significant benefit could be achieved. Other studies demonstrated that Hb responses were associated with improvement of quality of life (63). A recent study indicated that once weekly EPO dosing was as effective as TIW dosing (64). A large, open-label, trial demonstrated that this weekly regimen significantly improved quality of life as well as physical and mental health scores (65).

The Anaemia in HIV Working Group formulated evidence-based management strategies (63, 66). Anaemic patients with HIV infection should be treated with EPO after other correctable causes of anaemia have been ruled out and HAART therapy is initiated if appropriate. Only patients with endogenous Epo levels 1500 U/L should be treated. RHuEPO should be given SC at the dose of 100 U/kg TIW (three times per week) or 40,000 QW (once weekly). Dose increase up to 300 U/kg TIW or 60,000 QW can be considered in case of unsatisfactory response, but this strategy has not been formally proven to be effective. Target Hb values could be 13 g/dl in men and 12 g/dl in women. Many patients are likely to require iron supplements, presumably by the IV route, but this has not been studied prospectively (63).

Anaemia is a frequent complication of combination therapy with Interferon and ribavirin in patients with hepatitis C, resulting in discontinuation of treatment in a significant proportion of patients. Recent double-blind, placebo-controlled studies have shown that RHuEPO therapy 40,000 U/wk SC is also very effective in these patients, without altering the efficacy of anti-viral therapy (67, 68).

3.6 Chronic inflammatory diseases

Two small randomised trials have investigated the role of EPO in the anaemia of inflammatory bowel disease (IBD). The first trial demonstrated in a double-blinded fashion the superiority of iron + RHuEPO over iron alone (69). In the other placebo-controlled study of patients with Crohn's disease refractory to oral iron, IV iron + RHuEPO 150 U/kg TIW produced greater and faster Hb responses compared to IV iron alone (70).

Several randomised, placebo-controlled, studies of EPO therapy have been conducted in patients with rheumatoid arthritis, using a variety of doses of IV or SC RHuEPO and showing variable improvements in Hb values (71-75). In the largest placebo-controlled trial, RHuEPO at a dose of 240 U/kg TIW significantly increased Hb and
decreased secondary scores for disease activity, including the number of swollen joints, pain score and patients' global assessment of disease activity (75). However, in many trials a significant proportion of the patients did not respond, most probably because of functional iron deficiency (71, 74), and supplementation with IV iron-sucrose increased the response rate to 100% in those given iron (76). Several studies have shown that in addition to correction of anaemia there is a correlation between the resolution of anaemia and improvement of symptoms and quality of life scores (75, 77, 78).

3.7 Surgery

3.7.1 Surgery in cancer patients
Several studies have examined the peri-operative use of EPO to prevent the development of anaemia and reduce the need for subsequent transfusions in cancer patients (36). Most studies provided evidence that EPO treatment has a positive impact on Hb levels and some of them gave supporting evidence that red cell transfusion requirements were decreased or prevented (79, 80). Other studies failed to find an effect on transfusion need (81, 82), but this may be because they were carried out in patients with gastro-intestinal tract cancer in whom iron deficiency is a frequent problem. Indeed, IV iron appears to be beneficial in this setting (80). A study in head-and-neck cancer patients also showed only a trend toward decreased transfusion requirements with EPO therapy (83). In patients undergoing radical retropubic prostatectomy, preoperative EPO is as safe and effective as preoperative autologous blood donation in reducing allogeneic transfusion requirements (84) and a 300 U/kg EPO dosing regimen on preoperative days 14 and 7 was as effective as a 600 U/kg regimen (85). In another study, those randomised to EPO + acute normovolaemic haemodilution experienced higher post-operative Hb values compared to those randomised to acute normovolaemic haemodilution alone or to autologous blood donation, but exposure to allogeneic blood was similar in all groups (86).

3.7.2 Surgery in other patients
A meta-analysis examined the efficacy of EPO therapy in reducing exposure to allogeneic blood in patients undergoing orthopaedic or cardiac surgery (87). The odds ratio for the proportion of patients transfused with allogeneic blood was 0.36 (CI 0.24-0.56) in orthopaedic surgery and 0.25 (CI 0.06-1.04) in cardiac surgery. In patients scheduled for orthopaedic or cardiac surgery, the dose, dose interval and treatment duration varied widely among the studies and it is very difficult to identify the most effective regimen (87, 88). In patients undergoing coronary bypass
surgery, an 8-day regimen (5 days before to 2 days after operation) of 150 U/kg was as effective as a 300 U/kg schedule (89). In patients undergoing major orthopaedic surgery, a daily regimen of 300 U/kg starting 14 days before surgery was more effective than the same dose administered from 6 days prior to surgery to 3 days post-surgery (90). While a weekly 600 U/kg regimen (4 doses) was at least as effective as daily 300 U/kg (15 doses) (91) and a 15-day regimen (10 days before to 4 days after operation) of 100 U/kg was as effective as a 300 U/kg regimen, although the later dose tended to decrease the risk of transfusion in patients with baseline Hb 10-13 g/dL (92). From the available literature, it is thus reasonable to advise the SC administration of weekly 600 U/kg rHuEPO 3-4 weeks before surgery (93). However, a recent study indicated that weekly rHuEPO 125 U/kg was as effective as 250 U/kg when given for 3-4 weeks before surgery (94). Consideration should be given to higher doses in patients with Hb values 10-13 g/dL or when time to surgery is 2 weeks or less (95).

3.7.3 Iron supplementation prior to surgery
The route of iron supplementation for preoperative stimulation of red cell production has been tested in small trials. One such randomised trial showed that IV iron 600 mg weekly for 3 weeks preoperatively in EPO-treated patients produced significantly higher Hb values than oral iron at some time points (96). Follow-up was over several weeks, but the difference between groups was statistically significant only at some of the time points. However, another study compared 2 doses of 200 mg iron-sucrose IV or daily oral iron in patients receiving EPO therapy for 14 days pre-surgery, and found no difference in efficacy, whereas iron supplementation alone had no effect (97). This issue thus remains open.

3.8 Autologous blood donation
A meta-analysis examining the effect of EPO therapy on the capacity of patients to donate autologous blood before elective surgery concluded that the odds ratio for the proportion of patients transfused with allogeneic blood was 0.42 (CI 0.28-0.62) for orthopaedic surgery and 0.25 (CI 0.08-0.82) for cardiac surgery (87). Among studies published later, lower doses of EPO, even with IV iron, will not increase donation of blood nor decrease the risk of allogeneic blood transfusion (98). In a later study using 3 doses of 300-600 U/kg, rHuEPO improved the capacity of patients to donate 5 units of autologous blood, but exposure to allogeneic blood was not significantly changed (99).

A mathematical model has been developed to simulate the need for red cell transfusions based on a pre-determined minimum Hct (100). For non-anaemic patients, large estimated blood losses must occur before the minimum Hct is
reached, requiring transfusions. Pre-operatively donating patients are more likely to be transfused earlier and more frequently than non-donating patients. When incorporating the impact of Hct increase with pre-operative EPO therapy into the model, the post-operative Hct is a function of the volume of blood lost and the patient’s blood volume, but is independent of the patient’s initial Hct (101). This indicates that EPO therapy alone may be most effective in patients with mild anaemia undergoing surgical procedures commonly requiring blood transfusion (expected blood loss ≥ 4 U) (95). Integration of both EPO therapy and autologous blood donation in this model would suggest that EPO therapy may be indicated to support autologous blood donation in patients scheduled for surgery with estimated anticipated blood losses of 1,500-3,000 mL, ≥ 4 U autologous blood requirements and initial Hct of 33-39% (95, 102).

Iron-restricted erythropoiesis is a limitation to autologous donation in EPO-stimulated erythropoiesis (103). The question of iron supplementation has not been appropriately addressed in studies of autologous blood collection with EPO therapy. Oral iron alone without EPO treatment was not very effective in supporting autologous blood donation (104) but IV iron was shown to be superior to no iron (105). IV iron alone was not efficient in anaemic, iron-deficient, cancer patients, whereas EPO + IV iron was (106). In anaemic patients, IV iron may be superior to oral iron in facilitating EPO-stimulated autologous blood donation and avoiding exposure to allogeneic blood (107). A program of EPO therapy 600 U/kg BW and collection of 6 RBC units over 3 weeks with oral iron results in an additional red cell production rate of 34 mL/day compared to 22 mL/day with placebo (108). Such 2.5-fold increase over baseline erythropoiesis is much lower than the 4-fold increase over baseline and 48 mL/day of additional RBC production achieved when a similar program is conducted with twice weekly IV iron (109). In this setting, the Hct remained relatively stable throughout a phlebotomy program of 12 units over 6 weeks (95% success rate), in contrast with a study of normal volunteers receiving higher doses of EPO together with oral iron where the Hct dropped by 10% and only 75% of the scheduled units were collected (110). Therefore, oral iron may be sufficient support for EPO-driven erythropoiesis in non-anaemic patients undergoing a program of moderate autologous blood donation, but IV iron may be required in anaemic patients or those undergoing a more aggressive phlebotomy program. However, this remains to be formally proven.

3.9 Intensive care
Several reviews of studies published up to 2003 identified 5 randomised studies evaluating the use of EPO therapy in reducing need for RBC transfusions in critically ill patients (111-113). The first 3 studies detected some erythropoietic response in the form of increased reticulocyte counts but failed to obtain reductions
in RBC transfusions or even to achieve higher Hb concentrations in the EPO group. A study conducted in 160 patients compared placebo to EPO 100 U/kg daily for 5 days starting on day 3 of admission to the intensive care unit (ICU), and then every 2 days for up to 6 weeks, with both groups receiving the same dose of iron (114). Although the cumulative number of RBC transfusions was lower in the EPO-treated group, there was no difference in the proportion of patients requiring transfusions, or in mortality or other adverse events. The same group then conducted a large double-blind multicentre trial in 1302 patients, comparing placebo to EPO 40,000 U SC once weekly for 3-4 doses starting on ICU day 3 (115). Patients receiving EPO were less likely to undergo transfusions (60% versus 50%) and there was a 19% reduction in the total number of RBC units transfused as well as an increase in Hb from baseline. However, there was no difference in mortality, adverse events, length of stay, ventilator-free days or re-admissions to the ICU. A more recent small trial in critically ill children with bronchiolitis resulted in a favorable reticulocyte response to EPO treatment but without any change in RBC transfusion requirements (116).

Therefore, 10 patients needed to be treated with EPO to prevent one patient from receiving a transfusion, and there was no demonstrable impact on clinical outcomes, clearly showing that this approach is not cost-effective (117). In addition, the fact that the final sample in the largest study represented only 13% of those initially eligible raises questions about feasibility of the approach (115, 117). Finally, if a restrictive transfusion strategy is utilized, it is likely that there will be less benefit for EPO therapy (111). Therefore, the use of EPO in critically ill patients cannot be recommended, although further efforts should be put into identifying subsets of patients who may benefit from it.

3.10 Chronic heart failure (CHF)

The experience in CKD patients has shown that EPO treatment of anaemia improves CHF, inducing regression of left ventricular hypertrophy and improvement of left ventricular geometry (118-120). A phase II trial (121) in NYHA class IV CHF patients refractory to maximal medical therapy showed anaemia correction as well as improvement in left ventricular ejection fraction (LVEF), NYHA class and need for hospitalization with EPO therapy. The same group subsequently conducted an open-label randomised controlled study in 32 patients with NYHA class III or IV, with EPO given at the dose of 4,000 U/wk SC to maintain the Hb around 12.5 g/dL together with IV iron (122). This trial confirmed the positive effect of EPO therapy on LVEF, NYHA class and the need for hospitalization, whereas the control group worsened on all accounts, including a tendency for more deaths. The same group confirmed similar findings in prospective follow up studies in diabetics or nondiabetics.
as well as in octogenarians (123). A recent single-blind, placebo-controlled study
demonstrated significant improvement in peak oxygen consumption after 3 months
of EPO treatment (5,000 units SC twice weekly) in 26 patients with NYHA functional
class III or IV CHF (124).

The treatment of anaemia in chronic heart failure thus appears promising but the
potential risks of long-term usage need to be evaluated in larger randomised
studies. These risks include hypertension, thrombosis, myocardial infarction and death,
which have been shown to be elevated in dialysis patients with heart disease treated
to a target haematocrit of 42%.

3.11 Prematurity
Clinical trials have shown that starting EPO therapy between the 2nd and the 4th
weeks of life at doses of ≥500 U/kg/wk for 6-8 weeks, with iron ≥3 mg/kg/d,
significantly stimulated erythropoiesis and diminished the need for transfusion (125).
A recent meta-analysis showed that the early use of EPO therapy (starting on days
3-5 of life) in the smallest and sickest very low birth weight (VLBW) (BW<1000
) infants decreases transfusion requirements and the proportion of infants
transfused, particularly after the 3rd week of life (126). It is also critical to limit
the Hb trigger at which transfusions are initiated and to reduce blood sampling
for laboratory tests. It is generally considered that daily supplements of 1-2 mg
folic acid and ≥6 mg/kg/day of iron by either the IV or oral route are required to
sustain response to EPO therapy (125, 127). Indeed preterm infants have incomplete
iron acquisition during pregnancy and enormous iron requirements, secondary to
greater growth rates (127). It is critical to meet the iron demand not only for
erthropoiesis but also for growth and development, including the central nervous
system. Although parenteral iron may be the best route for supporting EPO-driven
erthropoiesis, no long-term comparison between IV and enteral iron supple-
mentation is available (127).

3.12 Postpartum
There is limited data on the use of EPO for the treatment of postpartum anaemia.
A recent systematic review by the Cochrane group identified 6 randomised clinical
trials involving a little more than 400 women and comparing EPO therapy with iron
treatment alone or placebo (128). Some increase in Hb was noted when EPO
therapy was compared to iron alone but there was no apparent effect on transfusion
needs, most probably because of the small size of the trials. Interestingly, EPO therapy
increased the likelihood of lactation at discharge from hospital. The use of EPO to
correct postpartum anaemia in addition to IV iron therapy cannot be generally
recommended but can be decided on an individual basis.
4. Response modifiers and prediction of response (Table 2)

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<td>• Endogenous Epo levels</td>
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4.1 Functional iron deficiency
Iron deficient (ID) erythropoiesis may occur even if iron stores are normal or elevated (129, 130). This is called functional ID, defined as an imbalance between iron needs in the bone marrow (increased by EPO-stimulated red cell production) and iron supply by macrophages that may not be mobilized sufficiently rapidly (Figure 1) (131-133). Functional ID is a major factor limiting the efficacy of erythropoietic agents in CKD patients (134) and during autologous blood donation (135). Although this has not been specifically examined in other situations, there is every reason to believe that its prevalence is very high in other settings as well.
A number of biological tools can be used to assess the adequacy of iron supply to the bone marrow (Table 3) (131, 136). Functional ID can be suspected whenever transferrin saturation is decreased (<20%), the percentage of hypochromic red cells (HYPO) (137) is increased (>10%) or the Hb content of reticulocytes (CHR) (137) is decreased (<29 pg). The soluble transferrin receptor (sTFR) cannot be used to evaluate iron status during EPO therapy because it is more influenced by the level of erythropoietic activity than by iron supply to the bone marrow (138). Serum ferritin levels are directly proportional to storage iron but say nothing about functional ID.
Iron supplements can be provided either orally or intravenously (Figure 1). In patients treated preoperatively with or without autologous blood collection, oral iron may be as efficient as low-dose IV iron (97, 139). However, the experience in dialysis patients (140), predialysis patients (141), patients treated preoperatively (96),

Table 3: Laboratory findings in functional iron
| Normal or increased ferritin                           |
| Laboratory signs of Iron deficient erythropoiesis      |
| Serum iron < 60 µg/dl                                  |
| Transferrin saturation < 20%                           |
| Hypochromic RBC > 5%                                   |
| Reticulocyte haemoglobin content (CHR) < 29 pg         |
| Soluble transferrin receptor > 7 mg/L                  |
### Figure 1: Correction of functional iron deficiency by intravenous iron

<table>
<thead>
<tr>
<th>Macrophages (ferroin)</th>
<th>Plasma (transferrin)</th>
<th>Marrow (haemoglobin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NORMAL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>EPO THERAPY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPO + IV IRON</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
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<tr>
<td>IV iron</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBC iron</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iron</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**A. Normal:** When senescent red cells are phagocytosed (1) by macrophages, iron is recycled into a transit pool (2); part is stored as ferritin (hatched area) (3) and the rest is released (4) to plasma transferrin (5); iron is then taken up (6) by the erythroid marrow (7) to produce normal red cells. Iron supply (4) by storage cells matches iron demand (6) by the erythroid marrow and transferrin remains adequately (50-60%) saturated (black filling) by iron (5).

**B. EPO therapy:** The erythroid marrow expands due to the intense stimulation by EPO. The increased demand for iron cannot be matched by storage iron release; transferrin saturation decreases (<20%), the erythroid marrow becomes functionally iron deficient and new red cells are hypochromic.

**C. EPO therapy + IV iron:** The plain arrows represent recycling of red blood cell iron, as described in panel B in which the expansion of erythroid marrow by EPO causes functional iron deficiency. The additional iron provided by intravenous iron products (dotted line) is also first taken up by macrophages that process it to release iron from the iron-glycan complex. Iron is then available for release by macrophages to plasma transferrin. When added to iron recycled from phagocytosed red cells, this allows for correction of transferrin saturation (hatched area) and provision of sufficient iron for erythropoiesis. The erythroid marrow can further expand without limitation by the iron supply.

Patients with rheumatoid arthritis (142) and cancer patients (39) has clearly indicated that oral iron supplementation is not effective but that IV iron substantially improves response to EPO.

There are 3 major forms of IV iron on the market (iron dextran, iron gluconate and iron sucrose or saccharate) (143). Whereas iron dextran has been associated with rare but potentially fatal anaphylactic reactions (144), iron sucrose and iron gluconate have excellent safety profiles (145-147). Iron sucrose has the advantage...
of allowing higher iron doses to be given at once, because comparable doses of iron gluconate give more toxicity (146). IV iron should be withheld when transferrin saturation is above 50% and/or serum ferritin greater than 1,000 μg/L, in case of active sepsis (145) and should not be administered concomitantly with chemotherapy because this may enhance the toxicity of some chemotherapeutic agents (148). Specific guidelines for iron supplementation have been developed for CKD patients (16, 17) and recommendations have been suggested for cancer patients (149).

4.2 Inflammation
Numerous other potential causes of resistance to EPO have been identified in CKD (17, 24) or cancer (150) patients. In CKD patients, inflammation is increasingly being recognized as the major cause of resistance to treatment (usually defined as higher EPO doses required to maintain similar target Hb) (151, 152). Very little is known on the impact of inflammation in other settings, although any source of inflammation, be it related to surgery, trauma, infection or concomitant disorders is likely to interfere with response to EPO. Hence, it is not surprising that response to EPO requires higher doses in patients with HIV infection, cancer or rheumatoid arthritis and is very limited in ICU patients.

4.3 Endogenous Epo production
A model of erythropoiesis, based on Epo prevention of programmed cell death, is very relevant to the clinical use of EPO (14, 95): EPO therapy should be most effective when endogenous Epo levels are inappropriately low for the degree of anaemia, as best assessed by the O/P (observed/predicted) ratio (153), and pharmacologic doses should also be able to expand erythropoiesis in normal individuals but not in anaemic patients with adequately increased endogenous Epo production. Epo deficiency is a universal finding in CKD patients (1), premature infants (125, 154) and after allogeneic HSCT (155), all of which are associated with excellent response rates to EPO. Serum levels >500 U/L in HIV patients (61, 62), >200 U/L (when treated with EPO alone) or >500 U/L (when treated with EPO + G-CSF) in MDS (40) predict for failure. Patients with haematological malignancies respond poorly if serum Epo is >100 U/L (or 200 U/L in severely anaemic patients) or the O/P ratio is >0.9 (150, 156). Serum EPO should be measured at least 3 weeks after chemotherapy, unless falsely elevated values will be obtained (150, 155, 157).

4.4 Residual marrow function
Apart from the moderate inhibition of marrow erythropoiesis by cytokines in disorders associated with ACD, marrow function is well conserved in most diseases
benefiting from EPO therapy. This is not the case in cancer patients, particularly with chemotherapy. Therefore, cancer patients with low platelet counts have been found to respond poorly to EPO (158). Similarly, high transfusion needs before EPO therapy have been associated with a poor response to EPO in cancer (31, 158-160) or MDS (44, 45) patients.

4.5 Early indicators of erythroid expansion
Once EPO treatment is started, it is important to recognise early signs of erythropoietic response, because full Hb response may take 2 months. In untransfused patients, a Hb increment of at least 0.3-0.5 g/dL after 2 weeks of EPO therapy is a clear indicator of response. However, Hb increments are of little help in transfused patients or when EPO is given to prevent anaemia prevention. Changes in reticulocyte counts are not adequate because this may simply reflect output of shift reticulocytes rather than true expansion of erythropoiesis (150, 161, 162). An increase in soluble TFR of >20% after 2 weeks is an excellent indicator of erythropoietic response (150, 161, 163).

4.6 Predictive algorithms
Predictive algorithms of response could help select patients and avoid prolonged ineffective use of an expensive medication in situations where there is a low probability of response. A predictive algorithm of response to EPO was first proposed in the early days of treatment of the anaemia associated with renal failure (161), illustrating the importance of inflammation, functional ID and early erythropoietic response. However, early prediction of response is not really necessary when response rates are very high, such as in CKD patients, premature infants, before elective surgery or after conventional allogeneic SCT. For the prevention of allogeneic blood transfusions during elective surgery, anaemic female patients with expected blood loss ≥2 L are the most likely to benefit (95). In cancer patients (150, 156, 164), the best algorithms combine an assessment of the adequacy of endogenous Epo production (at least in haematological malignancies) together with some early indicators of erythropoietic marrow response (changes in Hb or sTFR) (162, 163, 165). Selection criteria for MDS patients (40, 44, 45) have been described above. However, most predictive algorithms including all relevant parameters have not yet been validated in large prospective trials.

5. Side effects

5.1 Hypertension and seizures
The risk of hypertension is significantly increased in CKD patients receiving EPO
therapy, often requiring initiation or intensification of anti-hypertensive therapy. In cancer patients, a meta-analysis revealed a 1.25-fold increased risk of hyperton
tension (27, 28). In other indications, hypertension has not been reported. The incidence of seizures in CKD patients is in fact reduced by EPO therapy, while the risks of
headache, loss of dialyser clearance and hyperkalaemia are not affected (16, 20).

5.2 Platelets and thrombosis
EPO therapy increases platelet reactivity, improves function (166) and slightly
increases platelet counts (167) in CKD patients. An increased risk of thrombosis has
not been reported in most indications. In CKD patients, there is a possible increase
in the risk of thrombosis of the vascular access; there is some indication that it is
elevated in patients bearing polytetrafluoroethylene grafts but not in those with native
erteriovenous fistulae (16). A recent meta-analysis in cancer patients (27, 28) has
shown a small but not significant increase in the relative risk for thrombo-embolic
complications (RR = 1.58, CI = 0.94-2.66), representing an approximate incidence
of 6% compared to 4% in untreated patients.

5.3 Pure red cell aplasia
Pure red cell aplasia (PRCA) is a rare complication of EPO therapy due to EPO-induced
antibodies which neutralize all currently available EPO preparations as well as
denogous Epo (168, 169). Between 2001 and 2003, the estimated exposure-
adjusted incidence per 100,000 patient-years was 12 cases for Eprex® without
albumin, 6 for Eprex® with albumin, 1 for Neorecombin® and 0.2 for Epogen® (170).
PRCA occurred almost exclusively in CKD patients receiving SC Epoetin-α in Europe
(169, 170). In 2003 it was advised that patients with chronic renal failure should
not be given subcutaneous EPO and that particular attention should be paid to storing
the product at the recommended temperature of 2-8°C, following which the number of
cases has dropped dramatically (168, 171). The median delay between the start
of EPO treatment and the occurrence of PRCA is about 11 months (172). Standardised
diagnostic criteria have been proposed (173). When a case is suspected, all forms
of EPO should be immediately discontinued. Recovery can be obtained with
immunosuppressive therapy in 80% of the cases (171, 172). There is apparently no
relapse after stopping immunosuppressive treatment but it is unclear whether EPO
treatment can be safely resumed at some later stage (171, 172).

5.4 Tumour growth and survival
The discovery of erythropoietin receptors (Epo-R) on some tumor cell lines (174,
175) together with observations from two clinical studies (37, 38) have raised the
concern that EPO treatment could promote tumor growth and decrease survival. A trial in non-anaemic patients with metastatic breast cancer was stopped because of higher one-year mortality in the EPO arm. However, these patients had more adverse prognostic factors (38). The second study, in head and neck cancer patients receiving postoperative radiotherapy, showed diminished progression-free survival in patients receiving EPO (37). However, the placebo group had a Hb of 12.9 g/dL ("ideal" for tumor oxygenation) and the EPO group was overcorrected to 15.4 g/dL, suggesting that blood viscosity and microthrombosis led to reduced tissue oxygenation and poorer survival. Virtually all animal models indicate that EPO therapy does not promote tumor progression in vivo and many demonstrate that EPO treatment actually inhibits tumor growth rather than promoting it, whether used alone (176) or in conjunction with chemotherapy or radiotherapy (177). A recent meta-analysis by the Cochrane group concluded that there is suggestive but not definitive evidence that EPO treatment may improve overall survival of cancer patients (27, 28).

Therefore, it appears that the simple correction of anaemia may have beneficial effects in this respect, but that excessive stimulation of erythropoiesis with consequent polycythaemia should be avoided. Ongoing controlled trials in several well-defined groups of patients undergoing uniform treatment should provide us with a definitive answer on the survival question (Table 4).

<table>
<thead>
<tr>
<th>Side effect</th>
<th>EPO therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>yes, mostly in patients with poor kidney function</td>
</tr>
<tr>
<td>Seizures</td>
<td>no</td>
</tr>
<tr>
<td>PRCA</td>
<td>very low risk, almost only with IV Epoetin in chronic kidney disease</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>possible small risk increase in cancer and chronic kidney disease</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>no</td>
</tr>
<tr>
<td>Tumour growth</td>
<td>no clinical evidence</td>
</tr>
</tbody>
</table>

PRCA = pure red cell aplasia

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