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Endogenous Erythropoietin in the Anemia of Chronic Disorders

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INTRODUCTION

Anemia of chronic disease (ACD) is defined as the anemia associated with infection, inflammation, cancer, or trauma that has the characteristic picture of hypoferremia, hyperferritinemia, decreased transferrin concentration, and increased iron stores (1). The pathogenesis of ACD involves the combination of a shortened erythrocyte survival in circulation with failure of the bone marrow to increase red cell production in compensation (2–7). Inappropriate red cell production is itself related to a combination of factors, including impaired availability of storage iron, inadequate erythropoietin (Epo) response to anemia, and overproduction of cytokines, which are capable of inhibiting erythropoiesis (2–5). These cytokines are involved in the retention of iron in the reticuloendothelial system, gastrointestinal tract, and hepatocytes. They may interfere with Epo production by the kidney, and may exert direct inhibitory effects on erythroid precursors (3,4,8–12). Indeed, their effect is much wider, involving the whole hematopoietic system (13).

Cancer is one of the leading causes of ACD. However, the anemia observed in cancer patients may have multiple mechanisms (2,14,15). Hemodilution may artificially dilute the red cell mass. Bleeding, autoimmune or microangiopathic hemolysis, hypersplenism, and hemophagocytosis may all reduce the red cell life span. Nutritional deficiencies, including iron, folate, vitamin B12, and global malnutrition, may impair red cell production. The bone marrow may be involved by metastases, necrosis, myelodysplasia, and autoimmune red cell aplasia. These various causes, not including the "anemia of chronic disorders," have been reviewed in detail elsewhere (16). Surprisingly, there are no reports on the relative proportion of cancer patients in general or of patients with any form of cancer, in particular, that present the typical features of ACD. In other words, the true incidence of ACD in cancer patients is completely unknown. Hence, the relevance of the biologic features of ACD to the overall erythropoietic activity of cancer patients remains elusive.

Furthermore, chemotherapy and radiotherapy have a major impact on the incidence and severity of anemia in cancer patients. Compared to untreated cancer alone, chemotherapy may double the incidence of anemia (17). The incidence and severity of anemia largely depends on the form of cancer as well as the type and dose intensity of chemotherapy administered to patients (18). This is also true in children where the incidence of chemotherapy-induced anemia may even be greater because of the nature of the cancer being

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In this review, we will examine the evidence for defective Epo production in patients with ACD. We conducted a wide literature survey on the topic and critically analyzed the papers identified in this search. Solid experimental data indicate that several cytokines interfere with Epo production. However, it is unclear how these data can be directly applied in vivo. Many clinical papers reporting serum Epo levels in various disorders associated with ACD, in particular in cancer patients, have methodological problems. Two major such problems can be identified. The first problem relates to the heterogeneity of the patients studied in terms of disease and stage of the disease, as well as the simultaneous inclusion of patients at diagnosis, during treatment and after completion of therapy. The second problem involves the interpretation of serum Epo levels in individual patients or in groups of subjects, with lack of appropriate controls and inadequate interpretation of Epo data.

Therefore, we will first present the experimental data on the effect of various cytokines on Epo production. Second, we will comment on appropriate methods allowing interpretation of serum Epo levels in patients. We will then review the evidence for defective Epo production in patients with ACD, focusing in particular on HIV (as a model of chronic infection), rheumatoid arthritis (as a model of chronic inflammatory disorder), and cancer. In the case of cancer, we will attempt to examine various diseases independently whenever possible, and we will try to delineate the respective roles of cancer itself and of chemotherapy. Finally, we will illustrate how baseline serum Epo levels can help predict response to recombinant human erythropoietin (rHuEpo) therapy.

EFFECTS OF CYTOKINES ON ERYTHROPOIETIN PRODUCTION (Table 1)

Peripheral blood mononuclear cells from patients with chronic renal failure released soluble factors that suppressed Epo production by HepG2 cells, but these factors did not appear to be TNF-α or IL-1 (24). Neopterin also induces a suppression of hypoxia-induced Epo synthesis in HepG2 cells in a dose-dependent manner (25). It has been reported that IL-1α, IL-1β, TNF-α, IFN-γ, and TGF-β inhibited, whereas IL-6 stimulated, cobalt-induced or hypoxia-induced Epo production at the mRNA level by the hepatoma cell line Hep3B (26,27). The inhibitory effect of IFN-γ was found to be additive to that of IL-1 and even synergistic with that of TNF-α, and was capable of preventing any response to IL-6 (27). The same inhibition of Epo gene expression and protein production was observed with the HepG2 line for IL-1 and TNF but not for TGF-β, IFN-γ, or IL-6 (28–30). Contrary to phorbol-ester-induced inhibition of Epo production, inhibition by IL-1β or TNF-α was independent of protein kinase C (31). Inhibition of hepatic Epo production by TNF-α appears to be mediated by the 55 kDa (TNF-RI) rather than the 75 kDa (TNF-RII) receptor (32). IL-1, TNF-α, and IL-6 also blocked hypoxia-induced Epo formation by the isolated rat kidney (29).

Cytokine-induced inhibition of Epo production by HepG2 cells is not mediated by impairment of hypoxia-induced factor-1 (HIF-1) whose activity is rather enhanced by IL-1β

Table 1 Effect of Various Cytokines on Epo Production by the Hepatoma Cell Lines Hep 3B and G2, by the Isolated Rat Kidney and in Vivo

	Hep 3B	Hep G2	Rat kidney	In vivo
IL-1	↓	↓	↓	↓
TNF-α	↓	↓	↓	
TGF-β	↓	=		= ↓
IL-6	↑	= ↓	↓	↑
IFN-γ	↓	=		

or TNF-α, while VEGF expression remains unaffected (33). Several cytokines stimulate inducible nitric oxide (NO) synthase gene expression in several tissues. It is therefore not surprising that NO donors dose dependently reduced Epo production in the HepG2 cell line, either by directly influencing the cellular redox state or by increasing reactive oxygen species in the cell (34). Indeed, reactive oxygen species, including H_2O_2, have been shown to suppress the in vitro synthesis of Epo (35). H_2O_2, whose production is reduced in hypoxic conditions, has been proposed as a potential signaling molecule between the oxygen sensor and the transcriptional machinery (35). Desferrioxamine and cobalt chloride antagonize the inhibition of Epo production by reactive oxygen species, by reducing the action of H_2O_2, and by interfering with its production and/or scavenging, respectively (36). Similarly, the antioxidant vitamins A, E, and C significantly increased Epo production by the hypoxic isolated rat kidney (37). While vitamin A also dose dependently increased Epo synthesis in Epo-producing hepatoma cell cultures, vitamins E and C had no such effects (37). In another experiment in which Epo synthesis by HepG2 cells was reduced by monocyte-conditioned medium as well as IL-1β, TNF-α, and IL-6, dexamethasone decreased cytokine secretion by monocytes but did not affect Epo production on its own (38).

Injection of bacterial lipopolysaccharide (LPS) or IL-1β to normoxic or hypoxic rats resulted in increased TNF-α mRNA and reduced Epo mRNA in the kidney, as well as decreased serum Epo levels (39). In vivo administration of TGF-β was associated with depressed serum Epo levels in one study (40) but not in another (41). Administration of IL-6 to cancer patients resulted in elevated serum Epo levels that paralleled the development of anemia (42). Treatment of patients with chronic active hepatitis B with interferon-α resulted in a transient increase in plasma Epo levels (43). The exogenous administration of rHuEpo to mice treated with IL-1 was able to correct the suppression of CFU-E as well as of other erythroid parameters (44–46). Erythropoietin could also reverse the anemia of mice treated with single injections of TNF (47) but not always when mice were continuously exposed to TNF (47–49). Exogenous Epo was nevertheless capable of preventing the anemia induced by TGF-β (40).

INTERPRETATION OF SERUM Epo LEVELS

What Is a Normal Epo Value?

Erythropoietin production is regulated through a feedback system between the bone marrow and the kidney, which depends on a renal oxygen sensor (50,51). The capacity of the kidney to respond acutely to hypoxia by increasing Epo production may be modulated by prior sensitization. Post-transfusion polycythemic mice exposed to hypoxia (52) or cobalt chloride (53) did not show the increased rate of Epo production observed in normal animals (52). Mice made polycythemic by exposure to intermittent hypoxia showed an apparent sensitization of Epo-producing cells to hypoxic stimuli, explaining their greater Epo response to acute hypoxia, dexamethasone, testosterone, or isoproterenol, compared to hypertransfused mice (54–56). This was true for renal but not for extrarenal Epo production (57).

Serum Epo levels may vary considerably (51,58). Levels are usually between 10 and 20 mU/mL in normal subjects, may decrease somewhat in primary polycythemia, but increase exponentially when an anemia develops below an Hct of 30–35% (59). Therefore, a serum Epo value must always be evaluated in relation to the degree of anemia (Figs.1 and 2) (51). In addition, it should be compared to appropriate reference subjects who should display a normal Epo response to anemia, including patients with iron deficiency or hemolytic anemia (see below). Erythropoietin levels inappropriately low for the degree of anemia are encountered not only in renal failure (60), but also in a number of other conditions, including the anemia of chronic disorders (2,3). Inappropriately high serum Epo levels are often observed in secondary polycythemia, a feature permitting its diagnostic separation from primary polycythemia (61).

Serum Epo levels increase exponentially in proportion to the degree of anemia. We thus constructed reference regressions representing the normal relationships between Hct on less capable of

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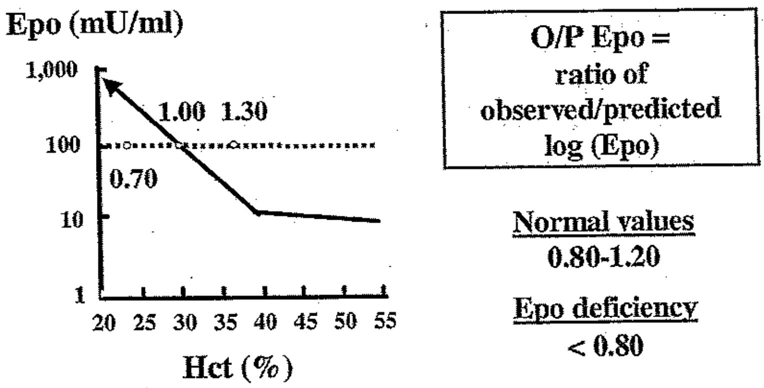

Figure 1 Interpretation of endogenous serum Epo levels. An individual serum Epo value of 100 mU/mL (dotted line) can be interpreted in relation with the degree of anemia through the O/P ratio. For an Hct of 30%, this Epo value is adequate (O/P ratio = 1.00), but for Hct of 23% or 37%, the same absolute Epo value would be defective (O/P ratio = 0.70) or excessive (O/P ratio = 1.30), respectively.

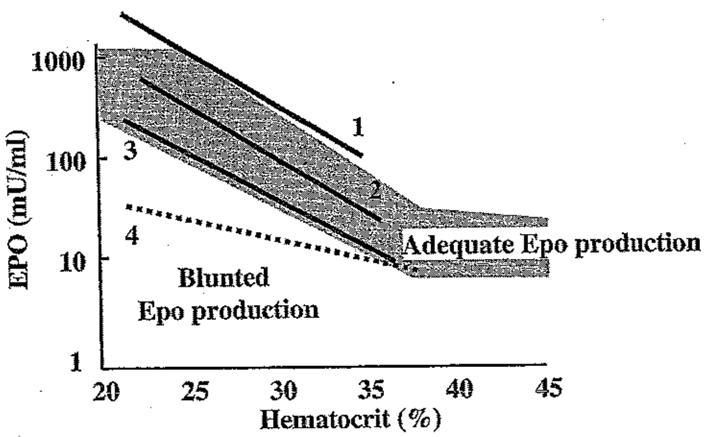

Figure 2 Interpretation of endogenous serum Epo levels. The hatched area represents the 95% confidence limits of the regression of Epo vs. Hct in an appropriate group of reference subjects, e.g., patients with IDA (2). However, serum Epo also depends on erythropoietic activity, with elevated and reduced levels in patients with low [aplastic anemia (1)] or high [thalassemia intermedia (3)] erythropoietic activity, respectively. A group of patients with ACD (4) shows a blunted Epo response to anemia.

one hand and Epo on the other, based on normal subjects and patients with hemolytic anemia (Fig. 2) (62). Two different regression equations were described for Hct > or < 40%. This cutoff Hct was chosen because it allowed for the best correlation for Epo data and because of literature data indicating that beyond such an Hct there is little modification of Epo levels. For Hct below 40%, the following regression ($R = -0.83$, $P = 0.0000$) was obtained between Epo (mU/mL) and Hct (%): $\log(\text{Epo}) = 3.420 - (0.056\ \text{Hct})$. For Hct over 40%, the regression equation ($R = -0.12$, NS) was: $\log(\text{Epo}) = 1.311 - (0.003\ \text{Hct})$. Based on these formulas, predicted log(Epo) values were derived for each Hct, O/P ratios of observed/predicted log(Epo) were derived, and 95% confidence limits were obtained in order to define a range of reference values for individual O/P ratios (Fig. 1). These limits are 0.80–1.20 for O/P Epo (62).

The adequacy of Epo production can thus be evaluated by two methods. When investigating a group of patients, this can be achieved by comparing patients and appropriate reference subjects by regression analysis (Fig. 2) (63). In this case, one should ensure that the study group encompasses a range of Hct values similar to that of the reference group; otherwise, the slopes of the regressions may be flawed. When studying an individual patient, the adequacy of Epo production can be evaluated by the O/P ratio (Fig. 1) (62). An O/P ratio below 0.80 indicates inadequate Epo production for the degree of anemia even if the absolute Epo value is high. It should be emphasized that the specific regression equations obtained in our study, on which O/P Epo ratios are based, cannot be automatically transposed to any other study. One must first either ensure that the Epo assay used yields Epo values similar to those measured in our Epo assay or construct one's own reference regressions with appropriate reference subjects.

Serum Epo Levels and Erythropoietic Activity

Many studies have reported higher serum Epo levels in patients with low compared to high erythropoietic activity

(Fig. 2). In an early study, urinary Epo secretion was similar in patients with marrow failure or hemolysis (64). The slope of the correlation between Epo and Hb was steeper for patients with iron deficiency anemia (IDA) compared to those with aplastic anemia or transient erythroblastopenia, because Epo values in moderately anemic subjects were higher in the latter group (65). For similar degrees of anemia, patients with aplastic anemia had higher serum Epo levels than patients with iron deficiency or hemolytic anemia (66). At any hemoglobin value, serum Epo levels in patients with pure red cell aplasia were fourfold higher than in those with IDA, and tenfold higher than in patients with megaloblastic or sickle cell anemia (67). In 34 patients with aplastic anemia, serum Epo levels were much higher than in patients with iron deficiency at similar degrees of anemia (68). The same conclusions were obtained in another group of 42 patients with idiopathic aplastic or Fanconi's anemia (69). One log higher serum Epo values were encountered in patients with erythroid hypoplasia or aplasia (erythropoietic activity <0.6 times normal) compared to subjects with thalassemia intermedia (erythroid activity >2 times normal) (70). To account for this effect of erythroid activity, serum Epo levels can be corrected by the ratio of the sTfR (a quantitative marker of erythropoietic activity) value in the patient relative to a normal sTfR value (70). High serum Epo levels are also observed transiently after intensive chemotherapy, whether followed by bone marrow transplantation or not, without concomitant change in hemoglobin or hematocrit (70–76). The peak Epo values are observed 7 days after transplant, i.e., about 14 days after the start of the conditioning regimen, at the time of the nadir of erythropoietic activity. Within 24–72 hr after starting IV iron therapy in patients with IDA, marked decreases in serum Epo were found before any change in Hb (70). Similar observations were obtained with rHuEpo therapy in pure red cell aplasia (70) with vitamin B12, or folate therapy in megaloblastic anemia (70,77–79).

These findings thus point to an inverse relationship between marrow erythropoietic activity and serum Epo levels: the higher the number of erythroid precursors, the lower the serum Epo value. As Epo exerts its action on target cells after binding to a specific Epo receptor (80), it is tempting to speculate that serum Epo levels may partly depend on the rate of Epo utilization by Epo receptor-bearing cells, primarily erythroid precursors (70,81). Similarly, marrow recovery after autologous stem cell transplantation (ASCT) would restore Epo utilization by erythroid cells, thus progressively returning Epo levels to a range appropriate for the degree of anemia (76). In patients with particularly fast engraftment, the duration of this correction phase is much shorter and may even finally lead to decreased Epo levels (76).

The idea that marrow utilization influences serum Epo levels was initially based on the observation that radiation-induced marrow hypoplasia was associated with a slower decline of serum Epo levels induced by hypoxia (82). However, the rate of Epo disappearance from the plasma of dogs with normal, hypoplastic, or hyperplastic marrow, was later shown to be similar, regardless of the experiment was performed in nephrectomized (83) or unmanipulated (84) animals. Nephrectomy or hepatectomy does not influence the pharmacokinetics of a large dose of native Epo (85) or a tracer dose of rHuEpo (86). Organ accumulation in the kidney and bone marrow of rats was minimal after intravenous injection of a tracer dose of rHuEpo (87,88). Furthermore, erythropoietin life span was similar in normal rats and in rats with bone marrow suppressed by cyclophosphamide or hypertransfusion or stimulated by hemolysis or bleeding (89). Similar conclusions were reached in mice 48 hr after initiation of hemolysis, bleeding or marrow suppression by 5-FU, or 2–24 hr after starting rHuEpo therapy, although the delay between induction of the desired experimental condition and measurement of Epo life span appears to be rather short (90). However, in normal human subjects (91,92) as well as in rats (93), the initial clearance of rHuEpo is decreased when the doses injected are increased, approaching a plateau at high doses. Furthermore, a surge in serum Epo levels after intense phlebotomy translates into decreased clearance of a tracer dose of rHuEpo (94). On the other hand, the pharmacokinetics of rHuEpo in hemodialysis patients was not different before and after 6 weeks of treatment with rHuEpo (95). In other studies, rHuEpo appeared to be eliminated from the plasma more rapidly after multiple doses than after a single dose in normal volunteers (96), whereas the elimination half-life of rHuEpo was increased on day 8 after two injections of rHuEpo to normal volunteers (97). The clearance of radiolabeled rHuEpo remained unchanged in rats injected with or without previous injections of unlabeled rHuEpo for 19 days (98) but was increased in sheep 8 days after experimental bleeding to Hb levels of 3–4 g/dL, before returning to baseline 4 weeks later (94). It was also progressively decreased in sheep following 5-FU- or busulfan-induced marrow ablation (99). Therefore, variations observed in serum Epo levels after intensive chemotherapy cannot simply be explained by changes in Epo consumption by the bone marrow.

The abnormal persistence of elevated plasma Epo levels in rats after cessation of intensive rHuEpo treatment given for 20 days could relate to suppression of erythroid activity (100). However, this was contradicted by our experiment with hypertransfused rats, in which polycythemia resulted in appropriate reduction rather than elevation of serum Epo levels, with subsequent depression of erythropoietic activity (100). Therefore, it is unlikely that persisting elevated Epo levels were due to nonutilization by a severely depressed erythroid marrow. Alternatively, Bozzini et al. (101) have suggested the existence of a yet unidentified feedback mechanism between Epo-responsive erythroid cells and Epo-producing cells. Cobalt- or hypoxia-induced Epo production in normocythemic mice is increased when erythropoiesis is acutely depressed and reduced when erythropoiesis is recently stimulated (101–103). Plasma Epo levels during hypoxia in mice with 5-FU- or irradiation-induced aplasia were higher than in normal mice (104). On the other hand, hypoxia-induced Epo response in transfused polycythemic mice is much higher when erythropoiesis has been previously stimulated for prolonged periods of time (101–103). These apparently contradictory observations in normal and polycythemic mice may be reconciled if it is a retracting erythron that can induce this Epo-hypersecretory state (101). However,

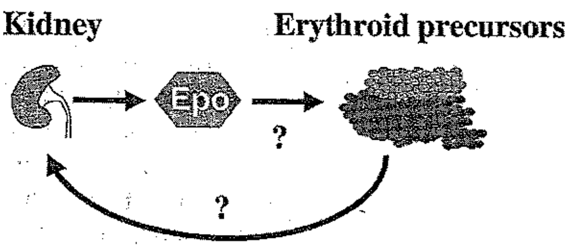

Figure 3 Serum Epo levels are the result of a balance between Epo production in the kidney and Epo utilization by the erythropoietic marrow. It remains to be determined whether the erythroid precursor mass acts directly by utilizing circulating Epo or indirectly by influencing the rate of Epo production.

although the erythron must shrink more after rHuEpo-than transfusion-induced polycythemia, it is unclear how hypoxia-induced Epo production would be relevant to our observed discrepancy in serum Epo levels between the two conditions.

In conclusion, serum Epo levels are the result of a balance between the rate of Epo production and its utilization by the erythroid marrow (Fig. 3). This should also be taken into account when interpreting the adequacy of a serum Epo value in various situations. Whereas it is indisputable that marrow erythropoietic activity independently influences serum Epo levels, it remains to be determined whether the erythroid precursor mass acts directly by utilizing circulating Epo or indirectly by influencing the rate of Epo production. Some other factors linking the erythron to Epo production may also exist. For instance, products resulting from red cell hemolysis may indirectly stimulate marrow erythropoietic activity as well as renal Epo production (105,106).

SERUM ERYTHROPOIETIN IN ANEMIA OF CHRONIC DISORDERS

Serum Epo levels have been examined in a variety of diseases associated with the anemia of chronic disorders. Rather than producing an exhaustive list of papers encompassing the whole spectrum of diseases that have been investigated for the adequacy of Epo production, we will focus on specific examples that have been particularly well documented. HIV infection will be taken as a model of chronic infection and rheumatoid arthritis as a paradigm for chronic inflammatory diseases. We will then turn to the more complex analysis of the data in the field of cancer.

Serum Epo in HIV Infection

Anemia is a common problem in human immunodeficiency (HIV) infection, being present in 70–95% of patients with AIDS, and frequently exacerbated by therapeutic agents such as zidovudive (107,108). Severe in vitro inhibition of erythropoiesis and transient stimulation of granulopoiesis are observed after bone marrow infection with various HIV isolates (109). Several papers have examined the adequacy of endogenous Epo response to anemia in AIDS patients. Serum Epo levels were elevated in HIV-seronegative and HIV-seropositive asymptomatic homosexuals and in patients with lymphadenopathy, AIDS-related complex (ARC) and AIDS, but were normal in asymptomatic HIV-seronegative or HIV-seropositive intravenous drug users (110). However, no attempt was made to correlate these Epo values to Hb or Hct values. Serum Epo levels were higher in HIV-infected subjects compared to normal individuals but again no control anemic group was available for proper evaluation (111). The regression line of serum Epo vs. Hb was quite similar in asymptomatic HIV-infected and uninfected 12-month old infants (112). HIV-infected subjects with AIDS or ARC not receiving zidovudine therapy exhibited a strong inverse relationship between serum Epo and Hb, but there was no comparison with a control group (113). In a group of 82 HIV-positive subjects, 41% of whom were receiving azidothymidine antiviral therapy, the slope of the regression of serum Epo vs. Hb was less steep than in a control group of patients with iron deficiency or aplastic anemia (114). However, few HIV-infected subjects were anemic and no details are available on the range of Hb values in the controls compared to the study subjects. There are only two papers for which the data can be fully interpreted and both indicate a blunted Epo production in patients with AIDS. Among 152 patients infected with HIV, anemia was present in 18% of asymptomatic, 50% of ARC and 75% of AIDS patients (115). The relationship between serum Epo and Hb disclosed a markedly blunted Epo response to anemia in AIDS patients compared to patients with IDA. The serum Epo–Hb relationship in a group of 42 patients with either ARC or AIDS, including 13 patients on zidovudine, closely resembled that of patients with the anemia of chronic disorders due to chronic infection, and both were considerably blunted compared to the relationship in subjects with iron deficiency (116). In addition, iron metabolism reflected a pattern of ACD with low transferrin saturation and elevated serum ferritin concentration. For any given degree of anemia, patients treated with zidovudine had significantly higher serum Epo concentration than zidovudine-naive patients (111,113,115). Indeed, the anemia associated with zidovudine therapy appeared to be due to red cell hypoplasia or aplasia (117). This occurred in the presence of elevated serum Epo values that again were not evaluated in relation to the degree of anemia in one study (117) but in another investigation even surpassed the Epo response of subjects with IDA (115). In conclusion, although the number of studies is limited, endogenous Epo response appears to be somewhat blunted in AIDS patients, but serum Epo levels are increased by zidovudine therapy.

Serum Epo in Rheumatoid Arthritis

The pathogenesis of anemia in systemic autoimmune diseases, including a possible defect in endogenous Epo production, has been reviewed elsewhere (118). In addition to the effect of cytokines on Epo-producing cells, vascular interstitial damage in the kidney peritubular cell area has been suggested as a cause of Epo deficiency in at least some of these systemic autoimmune disorders (118). There is some evidence for impaired erythropoietin response to anemia in rheumatoid disease (119).

Increased Epo levels were observed in RA patients that remained anemic over the years compared to nonanemic patients, but no appropriate control group was included in the study (120). In another study of 50 RA patients, serum Epo levels were slightly increased over normal values but "unrelated to low Hb concentration," but the data were not compared to an appropriate anemic control group (121). In a group of 14 anemic RA patients, serum Epo levels were significantly higher in those classified as IDA on the basis of absent iron stores in the bone marrow than in those classified as having ACD, but their Hb was a little lower as well (122). Among 58 patients with rheumatoid arthritis, 40 were anemic and 26 were classified as ACD and 14 as IDA (123). With similar average Hb values in the two groups, serum Epo concentration was slightly but not significantly higher in the IDA group. Within a group of 67 RA patients, 20 patients judged to have IDA based on reduced serum ferritin concentration had higher serum Epo levels than 24 other patients with normal or elevated ferritin concentration, while Hb values covered a similar range in the two groups (124). Among 136 patients with rheumatoid arthritis, 75 cases were anemic and a definitive cause was apparent in 65 of them (125). The majority ($n = 43$) had ACD and 15 had iron deficiency. Their Hb values were similar and correlated inversely with serum Epo, but Epo was significantly lower in those with ACD. Yet in another study, an evaluation of stainable bone marrow iron allowed the classification of 35 RA patients into ACD or IDA categories (126). A significant problem with all these studies is the absence of a control group with pure IDA instead of RA patients with IDA. The first of a few studies to compare RA patients with a control group with IDA came up with a relatively blunted Epo response to anemia in RA patients, but the control group did not have the same range of Hb values as the study group and the comparison is therefore not entirely valid (127). In another such study, serum Epo in both iron replete and iron deficient RA patients remained within the 95% confidence limits of the regression obtained in patients with iron deficiency or hemolytic anemia, but there was no clear inverse correlation with the Hb values in either group (128). However, the range of Hb values was obviously different in the control and RA groups, respectively. In a third study, among 97 anemic RA patients, serum Epo levels were lower in those with serum ferritin concentrations greater than 20 μg/L despite similar Hb values (129). In addition, at comparable Hb levels, serum Epo levels in RA patients with IDA were significantly lower than in IDA controls without RA. In another report, the average serum Epo value was lower in RA patients than in IDA controls at similar average Hb (130). In a final study, the Epo response to anemia was clearly diminished in patients with RA, both iron replete and iron deficient, compared to subjects with pure IDA (131).

On the other hand, in children with systemic-onset juvenile chronic arthritis (JCA), defective iron supply for erythropoiesis rather than inadequate endogenous erythropoietin production appears to be involved in the pathogenesis of anemia (132). Neither O/P Epo ratios nor regression analysis evidenced any defect in endogenous Epo production in this group of children. Indeed, in children with systemic, oligoarticular or polyarticular JCA, serum Epo levels were similar to those of patients with iron deficiency and similar degrees of anemia, while transferrin saturation was low and serum ferritin ranged from iron deficiency to considerably elevated values (133). Whereas severe anemia associated with active systemic-onset juvenile rheumatoid arthritis can be successfully treated with rHuEpo (134), this can also be achieved with IV iron alone (135). Some response to iron has been observed in RA as well (136). In addition, treatment of chronic disease in rheumatoid arthritis with TNF-α blockade resulted in dose-dependent Hb increments accompanied by a reduction of serum Epo concentration that suggest that TNF-α directly affected bone marrow precursors rather than suppressed Epo production (137).

In conclusion, rheumatoid arthritis patients often have blunted Epo response to anemia. This is much more prominent in those patients with other biological features of ACD than in those predominantly with IDA. However, these findings are not necessarily transposable to other systemic autoimmune disorders, as, for instance, children with juvenile arthritis have normal Epo response to anemia.

SERUM ERYTHROPOIETIN IN CANCER

Initial Studies

Earlier studies suggested that the anemia of inflammation produced in rats (138) and the anemia of cancer in mice (139) were accompanied by an inappropriate erythropoietin response for the degree of anemia. Similar conclusions were derived from studies measuring serum Epo levels by bioassay in patients with anemia secondary to chronic infection or malignancy, including Hodgkin's and non-Hodgkin's lymphoma, multiple myeloma, and solid tumors (140–142). However, this was not observed in other studies of tumor-bearing rats (143) and other human investigations found that serum Epo levels were diminished relative to expected levels only in patients with infection or inflammation but not in those with malignancies (144). Similarly, normal results were derived from studies of patients with cancer of the uterine cervix (145), renal cell carcinoma (146), and disseminated lung carcinoma (147).

When radioimmunoassays became available, a study showed that, compared to controls suffering from blood losses, iron deficiency, hemolysis or pernicious anemia, patients with hematologic malignancies under treatment with chemotherapy displayed a normal relationship between hematocrit and serum Epo levels (148). Similarly, in a mouse model of experimental melanoma, serum Epo concentrations remained adequate for the degree of anemia until terminal stages of the disease when the animals became severely cachectic (149). However, in a small group of patients with miscellaneous solid tumors, the average serum Epo value was less than in IDA controls with similar average Hb (130). An important study was conducted in 81 anemic patients with solid tumors in which it was found that for any given degree of anemia serum Epo levels were lower as compared to a group of control patients with IDA (150). In addition, the expected inverse relationship between serum Epo and hemoglobin was absent, but this was due to a small group of about 10 patients with inappropriate Epo response while all others were within the normal range.

In addition only 22 patients were untreated and it was shown that the Epo response was further decreased by chemotherapy, often including cisplatin. Adequate Epo production was restored in the presence of hypoxia but the possible role of infections in some patients was not addressed. With all these limitations, this study was taken as a landmark from which it is now widely believed that Epo production is defective in patients with cancer and that this is the major cause of anemia in them. However, the picture is much less clear than that.

Studies in Patients Scheduled for rHuEpo Therapy

Several investigations have been carried out in patients starting rHuEpo therapy. However, inclusion of many patients receiving chemotherapy may yield inaccurate conclusions about the adequacy of Epo production in cancer patients (see below). For instance, the majority of 12 patients with solid tumors selected for rHuEpo therapy, several of them receiving chemotherapy, had inappropriately low serum Epo levels (151). In a large study of anemic cancer patients selected to be treated with rHuEpo, Epo levels for any Hb value were significantly lower in patients receiving cisplatin-based compared to noncisplatin chemotherapy (152,153). In another trial of rHuEpo for cisplatin-associated anemia, serum Epo levels were said to be inappropriately low for the degree of anemia and not to correlate with hemoglobin levels, but no detailed data were available to substantiate this statement (154). A large study of transfusion-dependent chemotherapy-treated patients with multiple myeloma or low-grade non-Hodgkin's lymphoma showed that half of them had inappropriate Epo levels before starting rHuEpo therapy (155). This was also the case in another study of similar patients not requiring transfusions, in which the majority of the patients were found to have inadequately low serum Epo levels before the start of rHuEpo (156). In a multicenter study of patients selected for rHuEpo therapy for nonplatinum chemotherapy-induced anemia (157), serum Epo levels correlated inversely with baseline hemoglobin and appeared to be inappropriate for the degree of anemia only in a small minority of the patients. Another small study found inadequate Epo production as evidenced by low O/P Epo ratio in eight patients with lymphoma or multiple myeloma receiving chemotherapy, two of whom had mild degrees of renal failure (158). However, another investigation of six similar patients has found no evidence of defective Epo secretion in these disorders (159).

Solid Tumors

There are only few studies examining untreated patients with solid tumors. Among 84 such patients, only 13 were moderately anemic, and their serum Epo levels were slightly elevated but no control group was provided for comparison (160). In a group of 20 moderately anemic or nonanemic children with various solid tumors, serum Epo did not correlate with the degree of anemia but no control group was provided (161). Among 20 women with uterine or ovarian cancer, seven were anemic and their serum Epo relationship with the hematocrit appeared somewhat blunted (162). In 35 untreated patients with lung cancer, anemia was mainly due to impaired erythroid marrow response to erythropoietin stimulation, and a defect in Epo production was operative in only few of them (163). In a large cohort of 232 cancer patients, pretreatment O/P Epo ratios were decreased, apparently indicating defective endogenous Epo production (164). However, these O/E Epo ratios are not valid because the range of Hb values in the group of patients with IDA who served to derive the expected relationship between Epo and Hb was quite different from the one observed in cancer patients, many of them having quite normal Hb values. In a large study of 56 children with miscellaneous solid tumors examined before any treatment, careful comparison with an appropriate pediatric control group showed that serum Epo levels were adequate for the degree of anemia even if erythropoiesis (as assessed by sTfR levels) was significantly reduced, although to a lesser extent than in leukemic subjects (165). Among 92 patients with cirrhosis and hepatocellular carcinoma, 55 had anemia and 37 a normal Hb value (166). Virtually, all anemic subjects had serum Epo values in the range expected from the 95% confidence limits of iron deficiency controls, whereas only two of nonanemic subjects had inappropriately high serum Epo and polycythemia. Another investigation of 30 patients with hepatocellular carcinoma found no evidence of Epo deficiency (167).

Chronic Myeloid Disorders

The regulation of Epo production in patients with myelodysplastic syndromes (MDS) appears to be extremely variable. In a study of 14 patients, serum Epo levels were markedly elevated, and the slope of the correlation between Epo and hematocrit was similar to that reported for simple IDA (168). In another group of 46 patients, the slope of the regression was closer to that of controls with IDA than to that of controls with aplastic anemia (68). In a larger study of 75 MDS patients, there was also an overall inverse relationship between Epo levels and the degree of anemia (169). However, a wide range of Epo responses was encountered among patients with similar hemoglobin concentrations, and there were many patients with inappropriately low Epo levels as well as many others with inappropriately high values. A similar observation was made in another group of 46 patients with MDS who also had an overall inverse relationship between Epo and hemoglobin levels (170). A wide range of Epo responses between patients with similar hemoglobin concentrations was observed, with the highest values measured in those with less than 10% erythroblasts in the bone marrow. However, another investigation of 20 patients with MDS by the same group found no correlation between serum Epo concentration and total erythroid production, thereby negating any effect of the level of the erythropoietic activity on serum Epo concentration (171). The erythroid abnormality of patients with MDS was further analyzed in 19 nontransfusion-dependent patients (172). Serum Epo concentration was appropriate for the degree of anemia in 15/19 patients and was positively related to the percentage of highly fluorescent reticulocytes but not to the absolute reticulocyte count. Contrary to normal controls who exhibit a maximum concentration in the afternoon, a circadian rhythm of serum Epo concentration is not observed in MDS patients (173). Interestingly, higher serum Epo levels were associated with poorer survival but hemoglobin values were not provided, so it cannot be excluded that this is simply an effect of more severe anemia (174). Androgen therapy in MDS (and a few aplastic anemia) patients has been associated with a significant increase in serum Epo compared to untreated patients and even more so to iron deficiencycontrols, although the slope of the Hct vs. Epo regression was not different (175). Finally, patients with paroxysmal nocturnal hemoglobinuria have serum Epo levels that, for any given degree of anemia, are elevated compared to IDA patients but similar to those with aplastic anemia (176,177).

Among 61 anemic patients with myelofibrosis with myeloid metaplasia, inappropriately low levels of serum Epo were only found in eight patients (178). An inverse correlation was observed between serum Epo concentration and hemoglobin as well as between the O/P Epo ratio and ferrokinetic measurements of erythropoiesis. In four separate reports of 174 (179), 65 (180), 49 (181), and 40 (182) subjects with essential thrombocythemia, serum Epo concentrations were significantly below normal levels in many patients. However, these patients were generally not anemic, and their pattern was similar to that of 343 patients with polycythemia vera (179).

Leukemia and Lymphoma

Compared to patients with iron-deficiency anemia, serum Epo titers displayed similar inverse relationships with hemoglobin concentration in separate analyses of 47 patients with acute leukemia, 54 with non-Hodgkin's lymphoma, 34 with multiple myeloma, 16 with myelofibrosis, but curiously not in 19 with chronic myelogenous leukemia (68). However, the slope of the regression was blunted in lymphoma and myeloma patients, and several patients with multiple myeloma clearly had inappropriately low serum Epo levels. The O/P

Epo ratio was similar in patients with leukemia compared to healthy controls or patients with iron-deficiency anemia, indicating that serum Epo production was appropriate for the degree of anemia.

Other reports have focused on leukemias. Twelve patients with hairy cell leukemia were found to have a normal feedback mechanism for Epo production in response to anemia, but no formal control group was presented (183). The role of Epo in chronic lymphocytic leukemia (CLL) has been reviewed (184). Among 47 patients with CLL, Epo production was found to be adequate for the degree of anemia, and this conclusion was not altered in advanced stages of the disease (185). Inappropriate Epo levels were only found in three patients, two of whom had active infections. When patients with acute leukemia were compared with patients with ulcerative colitis, serum Epo levels were found to be higher for similar degrees of anemia and somewhat less well correlated with hemoglobin (186–188). Although ulcerative colitis represents a form of chronic disorder and therefore does not appear to be an ideal control group, this result at least indicated that there was no evident Epo deficiency in patients with acute leukemia. There are some studies of children with acute leukemia, in which it was also found that serum Epo was considerably increased and inversely related to hemoglobin concentration (189,190). In a large study of 55 children with acute leukemia examined at diagnosis, careful comparison with an appropriate pediatric control group revealed that erythropoiesis (as assessed by sTfR levels) was severely depressed, but serum Epo levels were appropriate for the degree of anemia in virtually all of them (165).

Finally, several papers analyzed Epo levels in patients with lymphoid malignancies. Erythropoietin production in response to anemia was considered normal in 12 children with lymphoma, but no formal control group was presented (161). Others examined the Epo–Hb relationship in 63 untreated patients with Hodgkin's disease and found no evidence for depressed serum Epo levels, as the minority of patients who had anemia responded with adequate Epo production (191). Erythropoietin production has been more precisely evaluated in multiple myeloma (192). A negative correlation between erythropoiesis and the degree of renal impairment has been observed (193–195). Using biological or radioimmunological assays, serum Epo levels were found to be appropriate for the degree of anemia when renal function was normal but inadequate when renal function was impaired (195–198). However, in another study, it was shown that serum Epo levels were inadequate not only in patients with renal impairment but also in a number of patients with normal renal function (63). Approximately 25% of all patients had defective Epo production and this increased to 30% of anemic patients, 50% of stage 3 patients, and 60% of those with renal impairment. Plasma viscosity may contribute to this phenomenon by blunting anemia-induced Epo production by the kidney (199).

Conclusions

In conclusion, few studies have been conducted in a way that definitive conclusions can be obtained, i.e., studies in untreated anemic cancer patients with a suitable control group to provide either comparison of regressions of serum Epo vs. Hct or Hb in the patient and control groups or O/P Epo ratios in individual patients. Most studies indicate that patients with leukemia or chronic myeloid disorders have appropriate Epo responses to anemia. A significant proportion of patients with multiple myeloma and possibly lymphoma have impaired Epo responsiveness. There is little evidence for defective endogenous Epo production in patients with solid tumors. However, there is no report specifically addressing metastatic vs. localized disease. Therefore, the overall incidence of Epo deficiency in solid tumor patients remains poorly defined.

SERUM ERYTHROPOIETIN AND CHEMOTHERAPY

Experimental Data

Experiments were conducted in various animal species to explore the effect of chemotherapy and total body irradiation on the capacity to increase Epo production in response to hypoxia. In rats exposed to hypoxia, neither cyclophosphamide nor sublethal irradiation modified Epo production significantly in the following days (200). Lethal irradiation led to anemia-driven Epo peaks that were not encountered in mice rescued by bone marrow transplantation (201). Administration of nitrogen mustard to sheep suffering from phenylhydrazine-induced hemolytic anemia produced considerably higher titers of serum Epo (202). Administration of vanadium to mice-bearing lymphoma was followed by prolonged enhanced Epo activity (203). Serum Epo levels during continuous exposure to hypoxia in mice with marrow aplasia induced by whole body irradiation or 5-fluorouracil injection were higher than in control mice similarly exposed (104).

These in vivo data apparently suggest an enhancing effect of chemotherapy on Epo production. As there are no preformed stores of Epo, this cannot be due to a sudden release of Epo by the kidney, mediated by cytostatic drugs. Some other speculations have been offered as explanation for this phenomenon (73). Cytotoxic therapy could cause a direct injury to the Epo-producing cells mimicking hypoxia. The blood flow to the kidney and/or liver could be altered so as to expose Epo-producing cells to hypoxia. As protein synthesis and gene transcription are necessary for the normal degradation of Epo mRNA, it is also possible that cytotoxic therapy could enhance Epo mRNA stability. However, some experimental data contradict these assumptions. The kidneys of dogs were isolated in situ and perfused with blood containing or not containing chlorambucil or thiotepa (204). Cobalt-induced Epo production was markedly suppressed 18–36 hr after the infusion of alkylating agents. In vitro studies were conducted to examine the effect of chemotherapeutic agents on Epo synthesis in cultures of the hepatoma cell line, HepG2. The RNA synthesis-inhibiting drugs daunorubicin, cyclophosphamide, ifosfamide, and CDDP, as well as the tubulin-binding agent, vincristine, dose dependently decreased production of erythropoietin. The DNA synthesis-inhibiting drugs methotrexate and cytosine-arabinoside did not have inhibitory properties (205,206). Together, these results indicate that chemotherapeutic agents may inhibit Epo production locally but that this effect is offset by other mechanisms, possibly nonutilization by a myelosuppressed bone marrow, leading to increased serum Epo levels.

Cisplatin (CDDP) is associated with a number of serious side effects, including nephrotoxicity and myelosuppression, in particular anemia of long duration (207). As cisplatin is associated with frequent and occasionally severe renal impairment, it has been speculated that Epo deficiency could be a major factor in the development of CDDP-induced anemia. Experimental data support this concept. RNA synthesis-inhibiting drugs, including CDDP, produced a dose-dependent decrease of Epo production by the human hepatoma cell line, HepG2, which partly correlated with cytotoxicity (205). In another study, CDDP also had a strong inhibitory effect on hypoxia- or cobalt-induced Epo mRNA expression and protein production in the Hep3B cell line, with no apparent cell damage (208). Five days after injection of CDDP to mice or rats, hypoxia-induced Epo production was not adversely affected in spite of severe tubular necrosis (209). However, another study reported a significant drop of serum Epo concentration and kidney Epo mRNA content in rats 4–14 days after receiving a bolus injection of cisplatin (210). Rats injected with a single high dose of CDDP developed acute renal failure and anemia that could be prevented or corrected by daily injections of 100 U/kg rHuEpo (211,212). In addition, there was a significantly greater recovery of renal function with increased tubular regeneration.

The most informative study was conducted by Matsumoto who compared the effect of 5-FU and CDDP on erythropoiesis in rats and the role of rHuEpo in this setting (213). 5-FU-induced anemia developed rapidly with a nadir at day 10, whereas the anemia caused by CDDP was less prominent and developed later with a nadir at day 21. In 5-FU-induced anemia, marked serum Epo elevation was observed at days 7–14. Although serum Epo levels correlated negatively with the hemoglobin, they fell rapidly afterwards, indicating that the early rise could be an effect of chemotherapy itself rather than anemia. This was followed by an increase of spleen but not marrow CFU-E and a rise in reticulocytes, followed by rapid correction of the anemia. In contrast, CDDP-induced anemia was not associated with changes in serum Epo or CFU-E values. As no animal decreased its hemoglobin below 13 g/dL, it is not surprising that serum Epo levels were not elevated around day 20. On the other hand, CDDP did not produce the early release of Epo into the circulation as observed with 5-FU. These results with CDDP were confirmed in another study (214). After injection of 5-FU, treatment with rHuEpo did not prevent the fall of hemoglobin but somewhat accelerated recovery in a dose-dependent fashion (213). Anemia could be completely prevented if rHuEpo was started one week before administration of 5-FU. After CDDP treatment, rHuEpo was very effective in correcting the anemia in a dose-dependent manner, even when started only 2 weeks after CDDP had been given (213,214).

Nonplatinum Chemotherapy in Patients

Several studies have been conducted in cancer patients. In six patients receiving intensive chemotherapy for acute leukemia, serum Epo levels increased substantially after treatment and gradually returned to baseline, often at the time of marrow recovery (71). Intensive chemotherapy given for induction of acute leukemia resulted in marked elevation of serum Epo concentration starting one or two days later and peaking after about 7 days, before normalizing later on (72). High serum Epo levels are also observed transiently after intensive conditioning before bone marrow transplantation without concomitant change in hemoglobin or hematocrit (70–76). Another small study observed a large increment of serum Epo soon after the initiation of chemotherapy for leukemia, which reached values of aplastic anemia patients at similar Hb levels (215). The same group reported the repeated postchemotherapy elevation of serum Epo levels in leukemic patients, pinpointing a nice reciprocal relationship with serum iron (216), and obtained similar findings in patients with lung cancer (217). After treatment with high-dose methotrexate, serum Epo increased in some children despite unchanged or even increased hemoglobin values, whereas after treatment with high-dose arabinoside cytosine, serum Epo increased markedly in all in response to decreasing hemoglobin (189). Similar observations were made in adults administered a 5-day course of 5-fluorouracil and leucovorin after the removal of colon cancer (218). Serum Epo levels progressively increased for 15 days in the presence of constant hemoglobin levels. Urinary Epo excretion also increases after chemotherapy (219). Patients with essential thrombocythemia on hydroxyurea, α-interferon or radioactive phosphorus therapy had increased Epo levels compared to untreated patients (180). All-trans retinoid acid treatment in patients with acute promyelocytic leukemia was also associated with a transient increase in serum Epo values that correlated inversely with reticulocyte counts, similar to the relationship between TPO and platelets (220). A single dose of cyclophosphamide also increases serum Epo levels in patients with vasculitis-associated hypertension, implying that the effect of chemotherapeutic agents is not limited to cancer patients (221). Whole body hyperthermia does not affect the serum Epo response to chemotherapy (222). Taken together, these results powerfully demonstrate a transient surge in serum Epo values during 1–2 weeks after chemotherapy.

Serum Epo levels after six cycles of non-nephrotoxic chemotherapy for stage 2 breast cancer increased slightly in relation to a small decrease in Hct and correlated negatively with insulin-like growth factor-1 (223,224). A large study reported the evolution of serum Epo and O/P ratios in 232 patients with miscellaneous tumors receiving a variable number of chemotherapy cycles, including cisplatin in 65% of the cases (164). While serum Epo increased progressively as an anemia developed in the majority of them, the O/P Epo ratio decreased until the fourth cycle and recovered at cycle 6. However, the relationship between serum Epo and Hb was fully maintained in 55 children with acute leukemia followed up at the end of induction and during the course of maintenance chemotherapy, whereas erythropoietic activity (sTfR levels) was further reduced compared to pretreatment levels (165). Identical conclusions were derived from the follow-up of 56 children with solid tumors (165). Pediatric patients investigated at various stages of induction, consolidation, and maintenance chemotherapy for acute leukemia maintained a significant inverse correlation between serum Epo and Hb that was particularly close in those with Hb less than 10 g/dL (225). These data suggest that nonplatinum chemotherapy in general does not induce Epo deficiency in the mid- or long-term.

Cisplatin Chemotherapy in Patients

In a study of 24 patients with gynecologic malignancies, there was a significant decrease of serum Epo levels between 2 and 6 hr after chemotherapy with cisplatin and cyclophosphamide, followed by a return to baseline values after 12 hr (226). Combination chemotherapy regimens based on cisplatin (100 mg/m^2) or carboplatin (300 mg/m^2) were associated with the usual peak of serum Epo levels observed 1–2 weeks after chemotherapy (227,228). Plasma Epo concentration increased similarly in advanced cancer patients 15 days after chemotherapy did or did not contain cisplatin (229). In seven patients with ovarian carcinoma undergoing cisplatin chemotherapy, serum Epo was increased 24 hr and 7 days later independent of concomitant anemia (230). In another small study, serum Epo in solid tumor patients receiving cisplatin was higher than in similarly anemic patients treated without cisplatin (231). Therefore, apart from a possible very early inhibition of Epo secretion, cisplatin is no exception to the development of a serum Epo peak 1–2 weeks after chemotherapy.

In patients with gynecologic cancer receiving multiple courses of combination chemotherapy including 50 mg/m^2 cisplatin, prechemotherapy serum Epo values were progressively elevated in relation with the degree of anemia achieved, although a comparison with only eight anemic controls is of little value (232). Few among head and neck as well as other cancer patients receiving cisplatin (100 mg/m^2)-based chemotherapy developed inappropriately low Epo levels, and there was no correlation with the amount of cisplatin administered or the degree of renal impairment (233). A linear relationship between log(Epo) and Hb was retained after treatment of 12 children with various solid tumors, but no comparison with pretreatment values or normal controls was provided (234). A longitudinal study of patients with ovarian or bladder cancer treated with nine courses of CDDP (60 mg/m^2) and doxorubicin (60 mg/m^2) showed progressive anemia correlating with renal tubular dysfunction (214). O/P Epo ratios declined progressively in proportion to the degree of renal dysfunction and recovered after cessation of CDDP therapy along with restoration of tubular function despite persistently depressed creatinine clearance. Overall, there is some evidence for Epo deficiency after completion of platinum-based chemotherapy, although this is certainly not a universal finding.

SERUM ERYTHROPOIETIN AS PREDICTOR OF RESPONSE TO rHuEpo

Based on our knowledge of the pathophysiology of the ACD and cancer, it is clear that the most useful approach is to treat the underlying disorder (2,14,15). However, red cell transfusions are regularly needed in patients with ACD. In this context, rHuEpo may be of particular value in stimulating endogenous erythropoiesis, and has now been widely tested in the treatment of ACD patients with a variety of diseases (235), including HIV infection (236), rheumatoid arthritis (237), and cancer with or without concomitant chemotherapy (155,156).

Theoretically, patients with a defect in the capacity to produce Epo would be more likely to respond to rHuEpo than those with adequate serum Epo levels for their degree of anemia. As Epo levels must be interpreted in relation to the degree of anemia, the ratio of observed-to-predicted Epo levels (O/P ratio) represents a better assessment of the adequacy of Epo production (62). In patients with hematologic malignancies, it has been observed that low baseline serum Epo levels (238) or decreased O/P ratios (158) were associated with a significantly higher probability of response. This has been confirmed in large multicenter trials in patients with multiple myeloma or non-Hodgkin's lymphoma (155,156). An O/P ratio < 0.9 was found to be associated with high response rates, whereas patients with an O/P ratio >0.9 rarely benefited from therapy (239). Studies in patients with solid tumors have failed to confirm such a consistent predictive value of baseline Epo even when Epo deficiency was demonstrated in part of the patients (151,153,154,157,240). However, a study aiming at preventing anemia in patients with ovarian carcinoma undergoing platinum-based chemotherapy showed a trend for lower transfusion needs in those with an O/P ratio < 0.8 (241). In addition, a small study in patients with a variety of solid tumors suggested that the ratio of baseline Epo/corrected reticulocyte count could provide some predictive information (242).

A combination of baseline parameters and early changes observed after 2 weeks of rHuEpo may provide another useful approach. Among evaluable patients treated in a large multicenter study (156), the failure rate was almost 90% when baseline serum O/P Epo was higher than 0.9 or when serum O/P Epo was less than 0.9 but the hemoglobin increment by week 2 was <0.3 g/dL. On the other hand, the success rate was around 90% when baseline serum O/P Epo was less than 0.9 and hemoglobin increased by ≥0.3 g/dL. Similar findings were obtained in a smaller study in children with solid tumors: an O/P ratio < 1.0 at baseline and a hemoglobin increment >0.5 g/dL after 2 weeks were associated with higher response rates (243). In another large single center study (239), the combined use of baseline serum Epo and the 2-week increment of sTfR proved to be very powerful. Only 18% of patients with a baseline serum Epo greater than 100 mU/mL responded to treatment, and only 29% responded when the baseline serum Epo was < 100 mU/mL but the 2-week sTfR increment was less than 25%. On the other hand, the response rate was 96% among patients with a low baseline serum Epo and a substantial sTfR elevation.

In conclusion, baseline serum Epo should be measured at baseline in patients with hematologic malignancies: treatment should not be initiated if endogenous serum Epo is above 100 mU/mL (or 200 mU/ml in severely anemic patients) or the

O/P ratio is >0.9. In addition, the best algorithms appear to be those combining an assessment of the adequacy of endogenous Epo production (at least in hematologic malignancies) together with some early indicators of erythropoietic marrow response (changes in hemoglobin or sTfR). Of importance, in patients treated with chemotherapy, serum Epo should be evaluated just prior to chemotherapy for its interpretation to be valid. Indeed, without any change in hematocrit, serum Epo may be inappropriately elevated in the 2 weeks after chemotherapy compared to prechemotherapy values, most probably because myelosuppression then decreases Epo utilization by target cells (see above). Therefore, it cannot be excluded that the failure to predict response in solid tumor patients may just be related to an inadequate timing of serum Epo sampling. While evaluation of endogenous Epo production may be relevant in various forms of anemia, it is of no interest in subjects in whom the aim of rHuEpo therapy is to prevent an anemia that is not yet present, in those in whom better tumor oxygenation before radiotherapy or induction of fetal hemoglobin is sought, or in disorders characterized by universal Epo deficiency.

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