Chapter 21

Prediction of response to rhEPO in the anemia of cancer

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Abstract

The anemia of cancer can be effectively treated with erythropoietic proteins, such as recombinant human erythropoietin (rHuEPO) alfa or beta or darbepoietin alfa in about 60% of the patients. However, the response rate varies according to treatment modalities as well as the response criteria used. A number of disease- or chemotherapy-related factors determine the probability of response. Several specific mechanisms of anemia, such as hemolysis, splenomegaly, bleeding, hemodilution, or ineffective erythropoiesis can seriously interfere with response. However, the type of tumor, in particular hematologic versus non-hematologic, is not critical, except in situations of major marrow involvement and limited residual hematopoiesis. Stem cell damage by previous therapy, reflected by low platelet counts or high transfusion needs, will impair response. In addition, marrow suppression by current intensive chemotherapy will also have a negative impact. Besides its intensity, the type of chemotherapy may not be critical, and patients undergoing platinum-based chemotherapy or nonplatinum regimens respond similarly. Complications such as infections, bleeding or nutritional deficiencies may have a major negative impact on outcome. An important response-limiting factor is functional iron deficiency, i.e. an imbalance between iron needs in the erythropoietic marrow and iron supply, which depends on the level of iron stores and its rate of mobilization. Therefore, intravenous iron supplements should be given when serum ferritin is below 100 ng/mL, reflecting the absence of iron stores, or when the transferrin saturation is below 20% or the percentage of hypochromic red cells above 10%, indicating functional iron deficiency even in the presence of adequate storage iron (normal or increased ferritin). Because up to 40% of the patients will not respond to rhEPO, it is of great importance to develop models that could help predict response to rhEPO and thus select the most appropriate cancer patients for this therapy. Most studies in patients with myeloma or lymphoma have indicated that patients with a low baseline serum EPO level will respond better, but

this is not so consistent in patients with solid tumors. Also of considerable interest are early changes of erythropoietic parameters after 2 to 4 weeks of treatment, including increments of serum transferrin receptor (sTfR), reticulocytes and hemoglobin. Combination of baseline serum EPO and the 2-week increment of sTfR or hemoglobin may provide the best prediction of response. Distinct predictive models should be used in patients with myelodysplastic syndromes. In these patients, the best models are different when rhEPO is used alone, with low baseline serum EPO, MDS other than RAS and transfusion independence predicting good response, or rhEPO together with rhG-CSF, with low baseline serum EPO and low transfusion needs predicting good response.

Introduction

Patients with solid tumors or hematological malignancies often develop anemia at diagnosis or in the course of the disease (Beguin 1996; Knight et al. 2004; Ludwig et al. 2004), particularly when given chemotherapy (Groopman et al. 1999; Ludwig et al. 2004). Many studies have shown that erythropoietin therapy, using recombinant human erythropoietin (rhEPO) alfa or beta or darbepoietin alfa, can ameliorate the anemia associated with cancer and chemotherapy, reduce the need for transfusions and improve quality of life (Bohlius et al. 2005). Clinical practice guidelines have been published to provide guidance on the use of rhEPO (Rizzo et al. 2002; Bokemeyer et al. 2004). However, as many as 30–50% of the patients do not respond even to very high doses of rhEPO. A number of factors may interfere with response to rhEPO in cancer patients, reflecting differences in disease- and treatment-related factors, but also large variations in dose, frequency and route of administration, duration of therapy and the response criteria used (Beguin 2001; Beguin 2002a; Beguin 2002b). It is therefore important to be able to recognize and correct conditions adversely affecting response to rhEPO, in particular functional iron deficiency. When no such particular condition can be identified, it would also be of great interest to have at one's disposal predictive algorithms of response. Thereby patients can be selected on the basis of their probability to achieve a good response to treatment, and prolonged ineffective use of an expensive medication can be avoided in those patients with a low probability of response. In this paper, we will review factors potentially affecting response to rhEPO (Table 1) and comment on the use of predictive algorithms.

Factors influencing response to EPO

Criteria of response

Before analyzing factors potentially affecting response to rhEPO, it is critical to define response criteria. Trials employing more favorable inclusion

Table 1. Factors potentially limiting response to rhEPO

Factor	Factor influences response significantly		Comments
	Yes	No	
Factors relating to rhEPO treatment			
• Dose	x		rhEPO: 450 U/kg/wk Darbepoetin: 2.25 µg/kg/wk
• Route	x		SC > IV
• Frequency		x	rhEPO: t.i.w. or weekly Darbepoietin: weekly or q 2–3 wks
• Duration	x		Needs at least 2 months
• Type of rhEPO		x	
Factors relating to the patient			
• Age		x	
• Sex		x	
Factors relating to the disease			
• Type of cancer		x	Possibly best in myeloma
• Marrow infiltration		x	Unless massive (acute leukemia)
• Mechanisms of anemia			
Hemolysis	x		
Bleeding	x		
Hypersplenism	x		
Marrow necrosis or fibrosis	x		
Hemophagocytosis	x		
Folate, B12, iron deficiency	x		
• Transfusion dependence	x		

Table 1. *Continued*

Factor	Factor influences response significantly		Comments
	Yes	No	
Factors relating to chemotherapy			
• Type of chemotherapy			
Platinum vs non-platinum		x	
Intensity of chemotherapy	x		Not effective if intensified chemotherapy
• Previous stem cell damage	x		Low platelet count, transfusion-dependence
Inflammation			*A major cause of treatment failure*
• Complications			
Infection	x		
Inflammatory disorders	x		
• Surgery	x		Bleeding + inflammation
Functional ID			*A major cause of treatment failure*
• Caused by ACD	x		
• Induced by rhEPO therapy	x		
Baseline parameters			
• Low platelet count	x		
• Neutrophil count		x	
• Hb, sTfR, reticulocytes		x	
• Creatinine		x	
• Transferrin saturation, ferritin		x	
• Cytokines		x	
• Serum EPO > 100–200 mU/ml (or O/P ratio > 0.9)	x		Hematological malignancies only?

Table 2. Response criteria

Cancer
- Hb response:
  - Hb increment ≥2 g/dL (Hct increment ≥6%) without transfusion
- Hematopoietic response: *either criteria*
  - Hb increment ≥2 g/dL (Hct increment ≥6%) without transfusion
  - Hb ≥12 g/dL without transfusion

MDS

1. *Nordic and French groups*
   - Complete response:
     - Hb ≥11.5 g/dL without transfusion
   - Partial response: *either criteria*
     - Hb increment ≥1.5 g/dL without transfusion
     - Hb stable without transfusion in previously transfused patient
2. *US, Italian, Spanish and German groups*
   - Good or major response: *either criteria*
     - Hb increment ≥2 g/dL without transfusion
     - No transfusion requirement in previously transfused patient
   - Minor or partial response: *either criteria*
     - Hb increment 1–2 g/dL without transfusion
     - 50% reduction in transfusion requirement

criteria and less stringent definitions of response are very likely to report better outcome. Therefore, uniform response criteria should be proposed for transfused and untransfused, severely or not severely anemic cancer patients. However, these criteria should necessarily be partly different when rhEPO is used for the prevention or the treatment of anemia (Table 2). Prevention means that rhEPO is used in a nonanemic patient to avert the occurrence of anemia after chemotherapy or other interventions. Treatment signifies that rhEPO is given to reverse an anemia that is already present. When treating anemia, a hemoglobin (Hb) response is defined by an increase in Hb by at least 2 g/dL (or increase in hematocrit (Hct) by at least 6 percentage points) from baseline without transfusion. However, when the entry Hb is 10–11 g/dL and the target Hb value 12–13 g/dL, such Hb response may not be achievable before reaching the target Hb and entering maintenance with lower rhEPO doses. Therefore, hematopoietic response can be defined as either an Hb response or an increase in Hb to >12 g/dL without transfusion. When rhEPO is given to prevent anemia, response criteria are less universally defined. A working definition of response could be a drop of Hb by less than 2 g/dL (Hct by less than 6 percentage points) without need for transfusion.

For MDS patients, some groups define a complete response (CR) as a Hb value >11.5 g/d/ and a partial response (PR) as an increase of Hb by at

least 1.5 g/dL or transfusion independence in combination with stable Hb in previously transfused patients. Others define a good or major response (GR) as an increase in Hb by at least 2 g/d/ or transfusion independence in previously transfused patients, and a minor or partial response by an increase of Hb by 1–2 g/dL or 50% reduction in transfusion requirements. The latter definition has been proposed as a standardized definition of response, but has yet to be widely applied (Hellstrom-Lindberg 2003, see chapter 20).

Treatment schedules (Table 1)

There is a clear dose-response effect with rhEPO and most studies in cancer patients have used doses of rhEPO in the range of 300–900 U/kg/wk, well above those given to renal failure patients. For instance, treatment of anemia in patients with advanced gastrointestinal cancer was much more successful with 10,000 U compared with 2,000 U TIW (Glimelius et al. 1998). In patients with metastatic breast cancer, 5,000 U TIW was more effective than 1,000 U TIW (Olsson et al. 2002). In patients with hematological malignancies, a dose of 2,000 U/d was associated with much lower response rates than 10,000 U daily (Osterborg et al. 1996). Daily doses of 5,000 U were more effective than lower doses and daily doses of 10,000 U did not bring about further improvement in anemic patients with myeloma or lymphoma (Cazzola et al. 1995). Similarly, darbepoetin alfa displays a dose-response relationship in the range of 0.5–4.5 µg/kg/wk in patients with lymphoid malignancies (Hedenus et al. 2002) or miscellaneous nonmyeloid malignancies (Smith Jr. et al. 2003), or in the range of 4.5–12 µg/kg/3 wks (but not beyond) in patients with solid tumors (Kotasek et al. 2003) receiving chemotherapy. However, a front-loading regimen of double-dose weekly darbepoietin alfa administered for 4 wks, followed by lower maintenance dose, decreased time to response, but overall response rates remained similar (Glaspy et al. 2003). Finally, weekly administration of a fixed or weight-based dose of darbepoietin alfa using a front-loading schedule result in similar hematopoietic responses (Hesketh et al. 2004).

The more convenient subcutaneous route of administration has been shown to ensure more favorable pharmacokinetics (Macdougall et al. 1989) that translates into higher efficacy in renal failure patients (Paganini et al. 1995). There is no known difference in the efficacy and safety profile of epoetin alfa (Janssen-Cilag) or epoetin beta (Roche) (Deicher et al. 2004). Although there is a lot of commercial fuss about comparisons involving data from observational studies, a recent study combining three randomized trials has shown that 40,000 U/wk rhEpo alfa and 200 µg/wk darbepoietin alfa can achieve similar Hb responses and impact on transfusions (Schwartzberg et al. 2004). Most trials administered rhEPO thrice weekly, a schedule demonstrated to be more efficient than daily injections in normal subjects

(Breymann et al. 1996). Although once-weekly dosing of 40,000 U epoetin alpha has been shown to increase Hb, decrease transfusions and improve quality of life in a fashion analogous to what is obtained with 10,000 U thrice-weekly administration (Gabrilove et al. 2001), it is only with epoetin beta that it has been formally proven that the same total dose of 30,000 IU given subcutaneously once weekly was at least as effective as 10,000 t.i.w. administration in anemic patients with lymphoproliferative malignancies (Cazzola et al. 2003).

Novel long-acting rhEPO molecules may also considerably prolong exposure to the active drug and thus improve the efficacy of therapy with fewer injections. One of these molecules is the "Novel Erythropoiesis-Stimulating Protein" (NESP) or darbepoetin alfa, which is produced by changing several amino acids in the rhEPO molecule in order to add additional carbohydrates and to prolong half-life by a factor of 3 while maintaining the same mechanism of action through receptor binding (Syed et al. 1998). Another long-acting rhEPO molecule named "Continuous Erythropoietin Receptor Activator" (CERA) incorporates a large polymer chain and is characterized by less tight binding to and different uptake by EPO receptor, resulting in a more potent erythropoietic activity and a considerably extended half-life. Once-every-3-wks schedules of CERA are currently tested in clinical trials in cancer patients (Dmoszynska et al. 2004; Dougherty et al. 2004; Österborg et al. 2004; Macdougall 2005).

The duration of treatment is of critical importance. In large clinical trials, whereas there is no significant difference in the rate of transfusions between placebo and rhEPO-treated patients during the first month of therapy, the difference becomes highly significant during the second and third months of treatment (Abels 1992; Glaspy et al. 1997). In one of these trials also, the efficacy of rhEPO appeared to be lower in cancer patients not treated with chemotherapy, because rhEPO was given for a shorter duration (and at a lower dose) (Abels 1992). This is because expansion of the erythropoietic marrow in response to rhEPO is very gradual and achieves maximum activity only after several weeks (Beguin et al. 1995). The response rate can thus be further improved when patients are treated for 6 months or more (Henry et al. 1994). In order to maximize "time with response", it would be desirable to achieve a faster response. Whether this can be achieved without increasing costs by providing higher doses of rhEPO for a short period of time (front-loading concept) followed by lower maintenance doses remains to be demonstrated (Glaspy et al. 2003; Hesketh et al. 2004).

Disease-associated factors (Table 1)

A number of mechanisms can be involved in the pathogenesis of anemia associated with cancer (Beguin 1996; Spivak 2005; Weiss et al. 2005, see chapter 6) and therefore interfere with response to rhEPO in individual

patients. Red cell loss may result from hypersplenism, blood losses consecutive to hemorrhage or iatrogenic phlebotomy, and autoimmune or microangiopathic hemolysis. Chronic or acute bleeding is a frequent complication of cancer, particularly in thrombocytopenic patients. Red cell production may be diminished by bone marrow infiltration, marrow necrosis, hemophagocytosis, myelofibrosis, deficiency of erythropoietic cofactors (folic acid, vitamin B12, iron), or infections. These mechanisms of anemia are much more prevalent in hematologic malignancies, but it is always important to identify them because specific therapeutic intervention can be effective. However, cancer-associated anemia is often delineated by the more general features of the so-called "anemia of chronic disorders" (ACD). ACD is a cytokine-driven condition characterized by inadequate production of EPO, inhibition of the proliferation of erythroid progenitor cells in the bone marrow and disturbances of iron utilization (Beguin 1996; Spivak 2005; Weiss et al. 2005).

Other factors have been examined. Age and sex have not been reported to influence response. Except when there is major invasion by cancer cells and limited residual normal hematopoiesis, marrow involvement by the tumor does not appear to limit the efficacy of rhEPO (Oster et al. 1990; Abels 1992; Musto et al. 1997; Littlewood et al. 2003), although this was found in one small study (Lastiri et al. 2002). The type of tumor has generally not influenced the response rate, provided that no other specific mechanism of anemia is at work. Patients with multiple myeloma or low-grade lymphoma apparently have similar response rates (Cazzola et al. 1995; Osterborg et al. 1996; Osterborg et al. 2002; Hedenus et al. 2003), except in one study where myeloma patients responded better (Hedenus et al. 2002). Although there were no apparent differences between hematologic and nonhematologic malignancies in the largest studies published (Abels 1992; Glaspy et al. 1997; Demetri et al. 1998; Glaspy et al. 2002), there has been a suggestion that patients with breast or colon cancer (Ludwig et al. 1993a), but not those with squamous cell carcinoma (Ludwig et al. 1993b), may respond less well than patients with myeloma, but this was not confirmed in larger studies (Demetri et al. 1998; Glaspy et al. 2002).

Chemotherapy-related factors (Table 1)

Anemia in cancer patients is often caused or aggravated by therapy with antineoplastic agents. In particular, treatment with platinum, but not with other chemotherapeutic agents, has been associated with impairment of EPO production (Wood et al. 1995). Patients who have been heavily pretreated with chemotherapy usually experience severe stem cell damage that could interfere with response to rhEPO (Musto et al. 1997), but other studies have not made the same observation (Demetri et al. 1998). As a matter of fact, the poorer response obtained in patients with lower platelet counts probably just indicates that (Cazzola et al. 1995; Osterborg et al. 1996; Osterborg et al.

2002). In addition, lower doses of rhEPO may be effective in patients with excellent platelet counts (Cazzola et al. 1995). Furthermore, transfusion-independent patients are more likely to respond than patients previously receiving transfusions (Demetri et al. 1998; Glaspy et al. 2002; Hedenus et al. 2002; Lastiri et al. 2002; Osterborg et al. 2002). Indeed, a meta-analysis of five randomized, double-blind, placebo-controlled trials in cancer patients receiving chemotherapy and epoetin alfa showed that being transfusion-dependent before rhEPO therapy was the most significant predictor for subsequent transfusions (Couture et al. 2005).

For patients treated concomitantly with chemotherapy, it is likely that response to rhEPO could be impaired in proportion to the intensity of the chemotherapy being administered. However, there is very little data in the literature to obtain evidence for such an effect. The negative impact of chemotherapy has been very well illustrated in animal studies in which rhEPO was much more "efficient" when it was started before the administration of 5-FU, because it could then increase the Hct better while myelosuppression was not occurring yet (Matsumoto et al. 1990). Patients receiving chemotherapy of moderate intensity respond as well as those not receiving concomitant chemotherapy (Abels 1992; Cazzola et al. 1995; Osterborg et al. 1996; Quirt et al. 2001). It is probable that more intensive chemotherapy regimens would be associated with lower response rates. In particular, rhEPO therapy is not capable to stimulate erythropoiesis in the early period following intensified chemotherapy with autologous stem cell transplantation (Link et al. 1994). Finally, responders to chemotherapy may also benefit more from rhEPO therapy than nonresponders (Bamias et al. 2003).

Multicenter studies have shown the same Hb response (speed and magnitude) in patients receiving platinum-based vs other forms of chemotherapy (Pawlicki et al. 1997; Demetri et al. 1998). Retrospective analyses of two large phase IV community-based studies (Glaspy et al. 2002), as well as of four prospective randomized trials (Littlewood et al. 2003) confirmed that the pattern of response was quite similar with these two forms of chemotherapy. In a large study (Abels 1992), patients receiving platinum-based chemotherapy responded more rapidly than those receiving other combinations but the overall response rate was similar in the two groups, whereas in other small studies patients receiving platinum chemotherapy responded a little better (Oberhoff et al. 1998; Lastiri et al. 2002). However, dose intensity of the two forms of chemotherapy was not assessed and it is therefore impossible to compare the degrees of myelosuppression induced by chemotherapy and, thus, the capacity of rhEPO to overcome it.

Functional iron deficiency

Iron requirements for erythropoiesis, and in particular EPO-stimulated erythropoiesis, have been increasingly recognized and red cell production may be

Table 3. Laboratory findings in functional ID

• Normal or increased ferritin
• Laboratory signs of iron deficient erythropoiesis:
Serum iron <60 µg/dl
Transferrin saturation <20%
Hypochromic RBC >10%
CHr <26 pg
Soluble transferrin receptor >7 mg/L
Erythrocyte protoporphyrin >70 µg/dl

limited by inadequate iron supply (Goodnough et al. 2000; Cavill 2002; Eschbach 2005, see chapter 26) (Table 3). Absolute iron deficiency (ID) is defined by the exhaustion of iron stores in macrophages and hepatocytes (Provan 1999). It is characterized by serum ferritin values decreased below the normal range. However, ID erythropoiesis and anemia may occur even if iron stores are not exhausted or are even elevated (Brugnara et al. 1993; Brugnara et al. 1994). This is called functional ID, defined as an imbalance between iron needs in the bone marrow and iron supply by macrophages (Fig. 1). This can be encountered in two different situations, corresponding to either decreased iron supply or increased iron needs. Iron release by macrophage is impaired typically by infection, inflammation or cancer (Beguin 1996; Spivak 2005; Weiss et al. 2005, see chapter 6). Iron needs are increased when marrow erythroid activity is stimulated, the best example being provided by rhEPO therapy (Brugnara et al. 1993; Brugnara et al. 1994). Macrophage iron, originating from normal or even elevated stores as well as from Hb-iron recycled when senescent RBC are phagocytosed, may not be mobilized sufficiently rapidly to match iron needs for the production of new red cells.

Functional ID is a major factor limiting the efficacy of erythropoietic agents (Fig. 1). It can occur before rhEPO therapy is started, either because iron stores are absent (absolute iron deficiency) or because storage iron release is impaired, a typical feature of ACD (Fillet et al. 1989). It can also develop in the course of rhEPO therapy when iron stores become progressively exhausted or more frequently when the increased iron needs of an expanding erythroid marrow cannot be matched by sufficient mobilization of often enlarged iron stores. Indeed, the vast majority of renal failure patients treated with rhEPO develop functional iron deficiency that limits seriously their erythropoietic response (Macdougall 1999). Similar observations have been made in patients receiving rhEPO to facilitate an aggressive program of autologous blood donation (Goodnough et al. 1998, see chapter 26). Although this has not been specifically examined in cancer patients treated with erythropoietic agents, there is every reason to believe that its prevalence is very high in this setting as well.

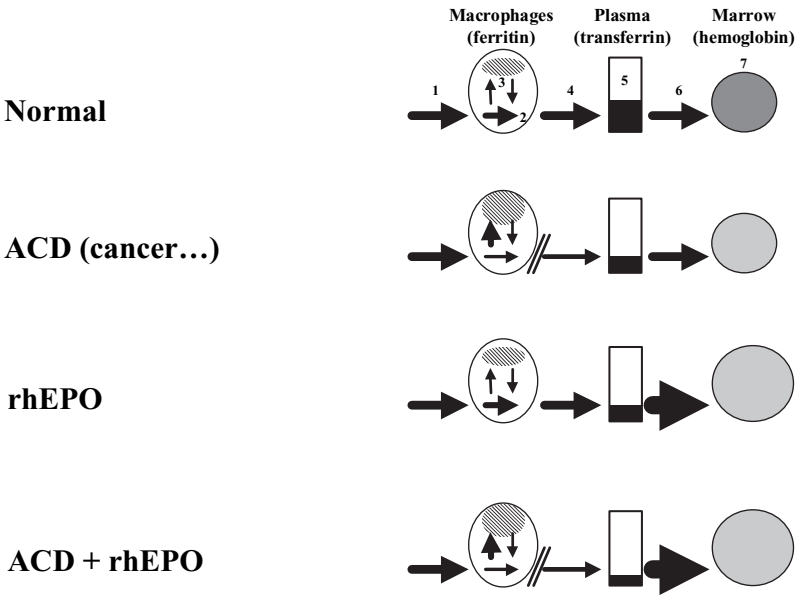

Fig. 1. Iron metabolism in conditions illustrating functional iron deficiency. A. *Normal*: when senescent red cells are phagocytosed (1) by macrophages, iron is recycled into a transit pool (2); part is stored as ferritin (hatched area) (3) and the rest is released (4) to plasma transferrin (5); iron 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 (20–40%) saturated (black filling) by iron (5). B. *Anemia of chronic disorder (ACD)*: iron release by macrophages is blocked and more iron is stored as ferritin within these cells. Iron supply can no longer match iron demand by the erythroid marrow: transferrin saturation decreases (<20%), the erythroid marrow becomes functionally iron deficient and new red cells are hypochromic. C. *Treatment with rhEPO*: the erythroid marrow expands upon intense stimulation by rhEPO. Its 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. D. *ACD treated with rhEPO*: impaired iron supply and increased iron demand combine to decrease transferrin saturation and cause functional ID

A number of biological tools can be used to assess the adequacy of iron supply to the bone marrow (Table 3) (Kaltwasser et al. 1999; Goodnough et al. 2000). Serum ferritin levels are directly proportional to storage iron in macrophages and hepatocytes (Worwood 1990). However, numerous conditions, including hepatic cytolysis, inflammation, and renal failure, are associated with falsely elevated serum ferritin levels. Indeed cutoff values for absolute ID can be as high as 40–120 µg/L instead of the classical 12 µg/L in situations such as renal failure or cancer. On the other hand, serum iron saturates serum transferrin to a certain degree and transferrin saturation is a

reflection of the equilibrium between iron supply and iron usage (Fig. 1) (Ponka et al. 1998). A soluble form of the transferrin receptor (sTfR) circulates in the plasma in proportion to the total body mass of cellular TfR (Beguin 2003). It is therefore largely influenced by the level of erythropoietic activity (through changes in the number of erythroblasts) and to a lesser extent by iron stores (through regulation of the number of TfR per cell) (Beguin 2003). However, as the impact of erythropoiesis quantitatively predominates, sTfR cannot be used as a marker of iron deficiency during rhEPO treatment (Beguin 2003). The percentage of hypochromic red cells increases over the upper limit of 5% when erythroblasts are deprived of adequate iron supply (Brugnara 1998). However, as reticulocytes are 20% bigger than mature red cells for the same amount of Hb, they are also hypochromic and high reticulocytosis should be taken into account in the interpretation of the percent of hypochromic red cells (Bovy et al. 1999; Bovy et al. 2004; Bovy et al. 2005). The Hb content of reticulocytes (CHr) will also decrease below 26 pg when the marrow does not receive enough iron to match its requirements (Brugnara 1998; Mast et al. 2002). As reticulocytes have a much shorter life span than red cells, the CHr will change much more rapidly than the percent of hypochromic red cells following the recent onset of iron deficient erythropoiesis (Brugnara et al. 1993; Brugnara et al. 1994).

Because there is some concern that tumor cells may need iron for optimal growth (Weinberg 1996), routine iron supplementation of all cancer patients receiving erythropoietic agents is not recommended. However, this should be balanced with the fact that transfusion of one RBC unit also provides a large amount (200 mg) of iron. Iron supplements should be given when absolute or functional ID is suspected (Fig. 2). The experience in iron-replete dialysis patients has clearly indicated that oral iron supplementation is not effective (Macdougall et al. 1996) but that IV iron substantially improves response when rhEPO therapy is instituted (Macdougall et al. 1996) and allows considerable (~40%) reduction in rhEPO dose requirements during maintenance (Ahsan 2000; Besarab et al. 2000; Johnson et al. 2001). In predialysis patients (Aggarwal et al. 2003) or in patients undergoing preoperative stimulation of erythropoiesis (Rohling et al. 2000) as well, the IV route of iron supplementation has proved superior to the oral route, but too low doses were not effective (Olijhoek et al. 2001; Stoves et al. 2001).

Iron usage has not been energetically pursued in clinical trials of erythropoietic agents in cancer patients and was generally left to the discretion of the individual investigator (Glaspy et al. 1999). In addition, iron has usually been given orally, a method proved to be of little efficacy in other settings and presumably even less effective in cancer patients because of impaired iron absorption, another characteristic of the ACD (Beguin 1996; Spivak 2005; Weiss et al. 2005). The safety and efficacy of IV iron to correct functional ID and improve anemia has been well documented in rheumatoid arthritis during rhEPO therapy (Vreugdenhil et al. 1992) or after failure of

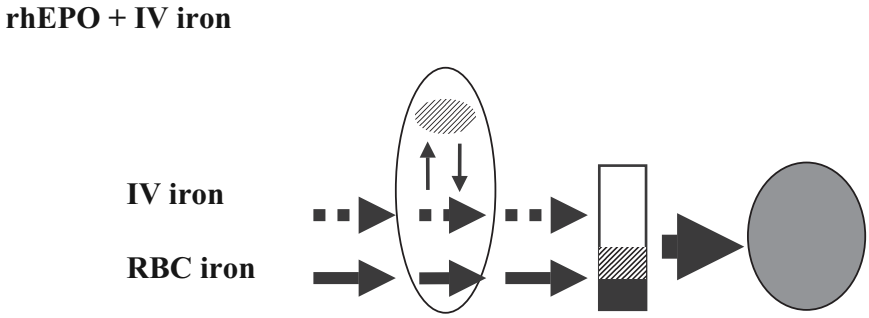

Fig. 2. Correction of functional iron deficiency by intravenous iron. The plain arrows represent recycling of red blood cell iron, as described in the third panel of Fig. 3 "rhEPO therapy" in which the expansion of erythroid marrow by rhEPO causes functional ID. The additional iron provided by intravenous 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. Adding up 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

oral iron in juvenile chronic arthritis, another form of ACD (Martini et al. 1994). A recent study in cancer patients undergoing rhEPO therapy has demonstrated that systematic IV iron supply clearly improved the early response to EPO and that oral iron was not effective (Auerbach et al. 2004). Despite many questions left unanswered (Beguin 2005), this study should be hailed as the first paper to address the question of iron supply during rhEPO therapy in cancer patients and should open the way for better designed clinical trials.

The safety of systematic IV iron supplementation has been demonstrated in renal failure patients under treatment with erythropoietic agents (Agarwal et al. 2002; Fishbane 2003; Afzali et al. 2004; Aronoff 2004; Van Wyck 2004). There are three major forms of IV iron on the market (iron dextran, iron gluconate and iron sucrose or saccharate) (Danielson 2004). All three compounds are primarily taken up by macrophages from where iron is released to plasma transferrin that transports it to the erythroid marrow (Fig. 2). Iron is very slowly released over a period of weeks from iron dextran complexes, allowing to inject very large doses of iron in a single infusion ("total dose infusion"), but much more rapidly from iron sucrose and iron gluconate complexes, so that their maximum tolerated doses are approximately 500 and 250 mg iron, respectively. On the other hand, iron dextran has been associated with rare but potentially fatal anaphylactic reactions (Bailie et al. 2005). The safety profile of iron sucrose (Yee et al. 2002) or iron gluconate (Fishbane et al. 2001) makes them the preferred IV compounds (Drueke et al. 1997).

Iron sucrose has the advantage of allowing higher iron doses to be given at once, because iron gluconate at comparable doses would be associated with more toxicity due to free iron release (Van Wyck 2004).

Because of limited data in cancer patients, recommendations can only be based on guidelines that have been published to provide treatment schedules with IV iron in renal failure patients (NKF-K/DOQi 2001b; Locatelli et al. 2004). An initial weekly loading dose of 100–300 mg IV iron could be recommended during the correction phase of the anemia, particularly, if there are signs of real or functional ID, while much lower doses (if any) are necessary during the maintenance phase. Iron supplementation should be targeted to maintain hypochromic red cells below 2.5%, CHr above 26 pg and transferrin saturation at 25–40%. To avoid toxicity from iron excess, IV iron should be withheld when transferrin saturation is above 50% and/or serum ferritin greater than 1,000 ng/mL, although the latter may not hold true in cancer patients. Oral iron should only be given to patients in whom IV supplements are not feasible or who do not tolerate them. Iron should be withheld in case of active sepsis (Aronoff 2004). Concomitant administration with chemotherapy, particularly anthracyclines, should be avoided, because transiently elevated transferrin saturation may enhance the toxicity of treatment (Link et al. 1996).

Inflammation

Besides functional ID, numerous potential causes of resistance to rhEPO have been identified in renal failure patients, but most of them are encountered only in small numbers of patients (Macdougall 2001; NKF-K/DoQi 2001b). However, inflammation has increasingly been recognized as the major cause of resistance to treatment (usually defined as higher rhEPO doses required to maintain similar target Hb) and efforts have been put into the identification of potential mechanisms (Macdougall et al. 2002; Del Vecchio et al. 2005). Infections have been shown to cause hyporesponsiveness to rhEPO (Danielson et al. 1995). Elevated baseline fibrinogen has been shown to predict failure of rhEPO therapy in hemodialysis patients (Beguin et al. 1993b). The weekly rhEPO dose was 80% higher in patients with C-reactive protein (CRP) >20 mg/L compared to those with lower values (Barany et al. 1997). Even intermittent CRP elevations could reflect chronic inflammation impairing response to EPO (Sezer et al. 2004). Indeed, in well-dialyzed and iron-replete patients, the acute-phase response, as represented by low serum albumin (a measure of both nutrition and inflammation) or high CRP in the context of high ferritin and low transferrin, was the most important predictor of rhEPO resistance (Gunnell et al. 1999). Malnutrition could also be a consequence of chronic inflammation (Del Vecchio et al. 2005). Induction of tumor necrosis factor alfa (TNF-α) (Takemasa et al. 2000;

Macdougall et al. 2002; Cooper et al. 2003b), Interleukin (IL)-10 (Macdougall et al. 2002; Cooper et al. 2003a; Cooper et al. 2003b), Interferon gamma (IFN-γ) (Macdougall et al. 2002; Cooper et al. 2003b), IL-12 (Macdougall et al. 2002), IL-13 (Cooper et al. 2003b), soluble TNF receptor p80 (Kato et al. 2001), decreased CD28 expression on T lymphocytes (Macdougall et al. 2002; Cooper et al. 2003a), but not soluble IL-2 receptor (sIL-2R) (Cooper et al. 2003a) or IL-4 (Cooper et al. 2003b), have been suggested as potential mechanisms. Findings have been less consistent with IL-6 (Kato et al. 2001; Cooper et al. 2003a). At the molecular level, the EPO signaling pathway in early erythroid progenitors, the so-called burst-forming unit erythroid (BFU-E), has been found to be attenuated in EPO-resistant patients as a result of dephosphorylation of STAT5 via upregulation of SHP-1 protein phosphatase activity (Akagi et al. 2004). These relatively EPO-resistant patients have a greater disease burden and in particular experience more infections (Kausz et al. 2005). Changing from conventional to ultrapure dialysis could reduce inflammation and hence decrease rhEPO dose requirements (Hsu et al. 2004). Following nephrectomy of a failed kidney transplant, patients demonstrated decreased inflammation and improved response to rhEPO (Lopez-Gomez et al. 2004). Treatment with the phosphodiesterase inhibitor pentoxyphilline could reduce T-cell expression of inhibitory cytokines and restore response to rhEPO (Cooper et al. 2004; Macdougall 2004).

Despite this wealth of evidence in renal failure patients that inflammation is a major factor impairing response to rhEPO, very little is known on the impact of inflammation on response to rhEPO therapy in cancer patients. Any source of inflammation, be it related to surgery, trauma, infection or concomitant disorders should interfere with response to rhEPO. Surgery is often followed by a transient loss of response to rhEPO, not only because it may be complicated by significant blood losses, but also because post-operative erythropoiesis is limited by the inflammatory effect of surgery on iron metabolism that impairs iron reutilization (Biesma et al. 1995). Infections occur frequently in cancer patients receiving chemotherapy. This should slow or totally prevent response at the beginning of rhEPO therapy as well as abrogate response when the target Hb is being maintained with lower doses, requiring higher doses to be started again.

Predictive models

Because response rates vary considerably among patients treated similarly and clinical efficacy cannot be assessed before weeks of treatment, identification of early predictors of response would be of major interest. The use of such prognostic factors of response could help provide the benefits of rhEPO therapy to as many anemic cancer patients as possible while avoiding prolonged ineffective use of an expensive medication.

Renal failure

A predictive algorithm of response to rhEPO has first been proposed in the setting of the anemia associated with renal failure (Fig. 3) (Beguin et al. 1993b). The best prediction by baseline parameters only was obtained with pretreatment soluble transferrin receptor (sTfR) and fibrinogen. Serum sTfR represents a quantitative measure of erythropoietic activity (Huebers et al. 1990) and is also increased when functional iron deficiency develops (Skikne et al. 1990). Soluble TfR is of particular interest in assessing response to rhEPO, including in patients with chronic renal failure (Beguin et al. 1987; Eschbach et al. 1992; Barosi et al. 1993; Beguin et al. 1993b; Beguin et al. 1994; Beguin et al. 1995; Ahluwalia et al. 1997; Mizuguchi et al. 1997; Lorenzo et al. 2001; Nakanishi et al. 2001; Bovy et al. 2004). There was a 100% response rate when both sTfR and fibrinogen were low, versus only 29% when there were both high, and 67% when one was low and the other high (Beguin et al. 1993b). The value of baseline sTfR was confirmed in another study (Ahluwalia et al. 1997). Indeed, higher sTfR levels in renal failure patients not receiving rhEPO therapy are often associated with functional iron deficiency (Fernandez-Rodriguez et al. 1999; Matsuda et al. 2002; Gupta et al. 2003). Changes of sTfR after 2 weeks of treatment were also predictive (Beguin et al. 1993b). When the 2-week sTfR increment was ≥20%, the response rate was 96%. When sTfR increment was <20%, the response rate was 100% when baseline sTfR was low and fibrinogen normal, 12% when baseline fibrinogen was elevated and 62% when baseline fibrinogen was normal but baseline sTfR high. In other studies as well, early sTfR increments correlate with later Hb responses (Beguin et al. 1995; Mizuguchi et al.

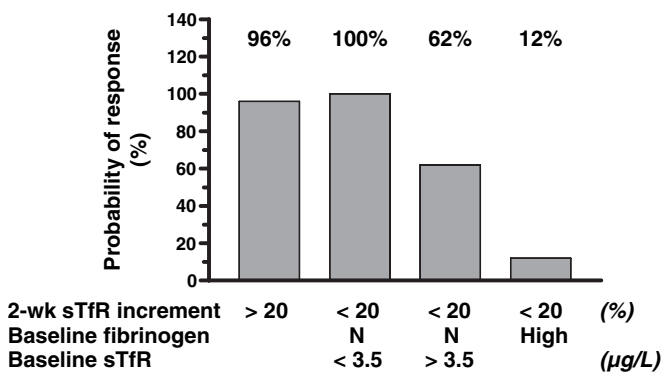

Fig. 3. Prediction of response to EPO in the anemia of renal failure by baseline sTfR (an indicator of functional ID), baseline fibrinogen (a parameter of inflammation) and the 2-wk sTfR increment (a marker of increasing erythropoietic activity) (Beguin et al. 1993b)

1997). The same is true for detecting an imminent Hb response to an increased rhEPO dose, which could be predicted with perfect specificity after 1 week based on a 20% increment of sTfR over baseline, but whose sensitivity could be increased when combined with changes in reticulocyte counts (Ahluwalia et al. 1997). Good (low baseline and large increment) and poor (high baseline and small increment) responders will thus have similar sTfR levels during treatment, so that such absolute levels cannot distinguish them (Hou et al. 1998). These prognostic factors illustrate the importance of the early erythropoietic response (changes of sTfR levels), subclinical inflammation (fibrinogen) and functional iron deficiency (baseline sTfR).

Baseline parameters

Serum EPO

Theoretically, cancer patients with a defect in their capacity to produce EPO would be more likely to respond to rhEPO than those with adequate serum EPO levels for their degree of anemia (Canadian Erythropoietin Study Group 1991). 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 (Beguin et al. 1993a). Based on regression equations obtained in reference subjects, predicted log (EPO) values can be derived for each Hct, and O/P ratios of observed-to-predicted values can be calculated (95% confidence limits 0.80–1.20) (Beguin et al. 1993a). In patients with hematologic malignancies, it has been observed that low baseline serum EPO levels (Ludwig et al. 1994) or decreased O/P ratio (Cazzola et al. 1992; Musto et al. 1997) were associated with a significantly higher probability of response to rhEPO. This has been confirmed in large multicenter trials in patients with multiple myeloma or non-Hodgkin's lymphoma (Hedenus et al. 2003; Cazzola et al. 1995; Osterborg et al. 1996), as well as in a combined analysis of several trials incorporating both patients with solid tumors and hematological malignancies (Littlewood et al. 2003). 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 (Cazzola et al. 1995; Cazzola et al. 1996; Osterborg et al. 1996). Even in patients with relative EPO deficiency (serum EPO <100 U/L), the lower the serum EPO, the higher the likelihood of response (Cazzola et al. 2003). In addition, in a single study that did not show a correlation between baseline EPO and Hb response, an association was still found between serum EPO and the later risk of receiving a blood transfusion despite darbepoietin alfa treatment (Hedenus et al. 2002). Nevertheless, 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

(Platanias et al. 1991; Abels 1992; Ponchio et al. 1992; Cascinu et al. 1994; Glaspy et al. 1997; Demetri et al. 1998; Glimelius et al. 1998; Oberhoff et al. 1998; Glaspy et al. 2002; Gonzalez-Baron et al. 2002; Lastiri et al. 2002). 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 (ten Bokkel Huinink et al. 1998). In another trial in patients with solid tumors undergoing platinum-based chemotherapy, baseline O/P ratio <0.9 was strongly associated with response (Bamias et al. 2003). Other studies in children (Leon et al. 1998) or adults (Fjornes et al. 1998) with solid tumors found baseline EPO to be highly predictive of response (Leon et al. 1998). 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 (Charuruks et al. 2001). Of importance, in patients treated with chemotherapy, serum EPO should be evaluated just prior to chemotherapy for its interpretation to be valid (Fig. 4). Indeed, without any change in Hct, serum EPO may be inappropriately elevated in the 2 weeks after chemotherapy compared to pre-chemotherapy values, most probably because myelosuppression then decreases EPO utilization by target cells (Beguin et al. 1991). Therefore, it cannot be excluded that the failure to predict response may just be related to an inadequate timing of serum EPO sampling (Glimelius et al. 1998; Osterborg et al. 2002), but most studies do not report when serum EPO was evaluated relative to chemotherapy.

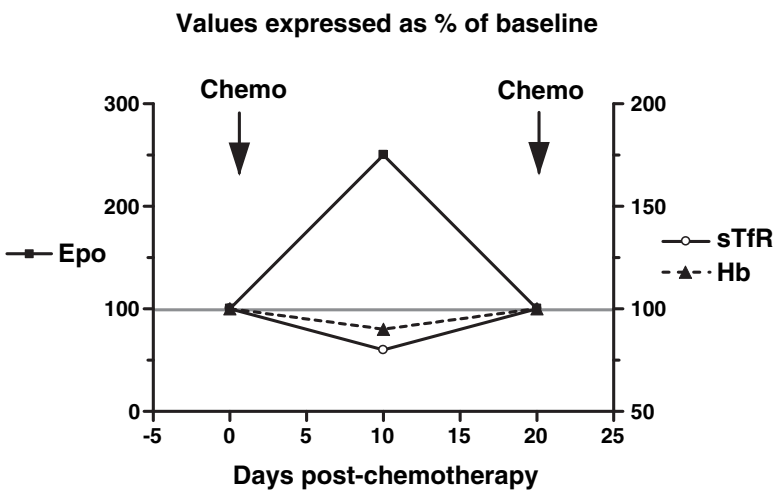

Fig. 4. Changes in serum EPO, Hb and sTfR after a chemotherapy cycle. Chemotherapy transiently causes an increase in serum EPO levels that is disproportionate to the degree of anemia

Other parameters

Other baseline parameters have been examined as possible predictors of response. Pretreatment Hct is of course an important factor when rhEPO is given for the prevention of anemia, but is no longer helpful when it is given after anemia is well established (Ludwig et al. 1994; Demetri et al. 1998; Glaspy et al. 2002; Gonzalez-Baron et al. 2002; Littlewood et al. 2003), even if a single study found an association between low baseline Hb and the risk of being transfused on study (Hedenus et al. 2002). Other measurements of erythropoietic activity, such as the reticulocyte count or sTfR levels were not predictive of response (Ludwig et al. 1994; Ludwig et al. 1994; Musto et al. 1997; Gonzalez-Baron et al. 2002; Littlewood et al. 2003). Patients with more BFU-E in the peripheral blood apparently respond better (Musto et al. 1997). Platelet counts below $50–100 \times 10^9$/L are usually (Cazzola et al. 1995; Osterborg et al. 1996; Osterborg et al. 2002), but not always (Ludwig et al. 1994), associated with poorer responses. Similarly, low neutrophil counts may be associated with a lesser probability of response (Cazzola et al. 1995), but this has not been found in most studies (Ludwig et al. 1994; Osterborg et al. 1996; Osterborg et al. 2002; Littlewood et al. 2003). Serum creatinine (Cazzola et al. 1995; Osterborg et al. 1996), except in one small study (Fjornes et al. 1998), is not predictive of response. Baseline ferritin below 400 ng/mL has been found to predict for good response in one study (Littlewood et al. 2003) but not other studies (Ludwig et al. 1994; Gonzalez-Baron et al. 2002), while high transferrin saturation has not predicted failure in most studies (Ludwig et al. 1994; Cazzola et al. 1995; Osterborg et al. 1996; Gonzalez-Baron et al. 2002; Osterborg et al. 2002), except one (Littlewood et al. 2003). Only large doses of rhEPO can overcome the strong inhibition of erythropoiesis induced by such cytokines as IL-1, TNF-α and IFN-γ. The results of a study evaluating the predictive values of serum levels of these cytokines were disappointing (Ludwig et al. 1994). This was confirmed by others (Lastiri et al. 2002). This is not entirely surprising since serum levels of these cytokines may not be relevant, whereas local intramedullary levels may be much more important but are very difficult to evaluate. However, others have observed that response was more likely in patients with low serum levels of TNF-α or IL-1 (Musto et al. 1997).

Early changes in erythropoietic parameters

Early changes in parameters of erythropoietic activity observed after 2 weeks of treatment could be more informative. A rapid elevation of Hb levels by 0.3–1.0 g/dL after 2–4 weeks often predicted a good probability of later response (Ludwig et al. 1994; Cazzola et al. 1995; Henry et al. 1995; Glaspy et al. 1997; Demetri et al. 1998; Glimelius et al. 1998; Quirt et al. 2001; Glaspy et al. 2002; Gonzalez-Baron et al. 2002; Littlewood et al. 2003). An Hb

increment of 0.5 g/dL after 4 wks was confirmed by a number of different statistical techniques to provide the best predictive power among several hematological and iron parameters (Gonzalez-Baron et al. 2002). An increase of reticulocyte counts by ≥40,000/μl from baseline to week 2 or 4 appeared to be predictive of response but its discriminative power was weak (Ludwig et al. 1994; Henry et al. 1995; Gonzalez-Baron et al. 2002; Littlewood et al. 2003) and it was not found in other studies (Lastiri et al. 2002). In several studies, hematologic response to rhEPO was strongly associated with early increases (20–25% over baseline) of sTfR levels after 1–2 weeks of treatment (Cazzola et al. 1992; Ponchio et al. 1992; Ludwig et al. 1994; Cazzola et al. 1996; Beshara et al. 1997; Musto et al. 1997; Beguin 1998a; Beguin 1998b). A study presenting the most comprehensive analysis found that increases of Hb, sTfR and reticulocytes, as well as decreases of serum EPO, ferritin, iron, CRP or neopterin after 2 weeks were all correlated with response to rhEPO (Ludwig et al. 1994). Apart from changes in Hb and CRP, changes in sTfR levels was the single best predictor of response among 63 parameters examined in univariate analysis at baseline and after 2 weeks, although it provided information redundant of the Hb changes. In another large series of patients, increase in Hb and reticulocytes as well as lower absolute values for ferritin and/or transferrin saturation after 2–4 wks were all associated with higher response rates to rhEPO (Littlewood et al. 2003). More recently, Hagberg at al. observed that healthy volunteers treated with rhEPO showed a more distinct increase in β-globin mRNA levels than in Hb, sTfR or reticulocytes, but this remains to be studied in cancer patients (Hagberg et al. 2003).

Predictive algorithms based on early changes

Various models have sought to combine the predictive power of several parameters. In a study including similar numbers of patients with solid tumors or hematologic malignancies, if after 2 weeks of therapy EPO was >100 mU/ml and Hb had not increased by at least 0.5 g/dL, there was a 94% probability of unresponsiveness; otherwise response was likely in 80% of the patients (Ludwig et al. 1994) (Fig. 5). If serum EPO was <100 mU/ml and Hb had increased by ≥0.5 g/dL, the probability of responses was 100%; otherwise the probability of failure was 62%. However, 34 out of the 80 patients evaluated did not fall into any of these two categories and thus prediction was valid only in a little more than half of the patients. The predictive value of a decrease in serum EPO levels may have two explanations. Endogenous serum EPO could decrease as the Hct rose in responders, but the magnitude of the Hct changes by 2 weeks seemed to be too small for that. On the other hand, EPO could be utilized by an expanding erythroid marrow or conversely accumulate in nonresponders, but it cannot be excluded that these later patients were receiving more intensive chemotherapy than others and thus

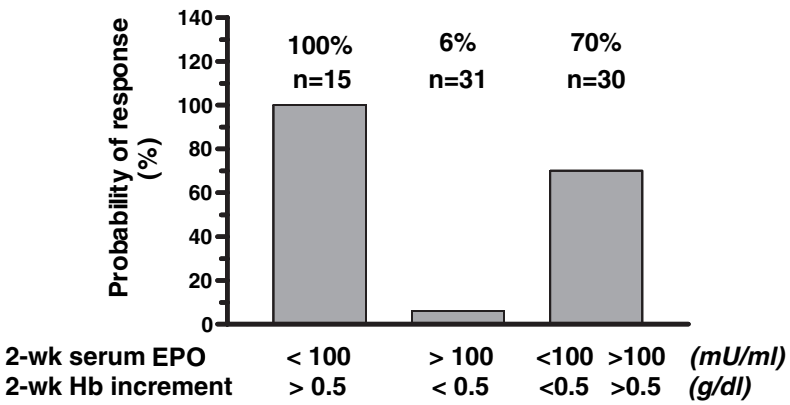

Fig. 5. Prediction of response to rhEPO in the anemia of cancer by the week-2 absolute serum EPO level and the 2-wk Hb increment (Ludwig et al. 1994)

be more likely to have inappropriate increases of endogenous serum EPO values (Beguin et al. 1991). Alternatively, a serum ferritin value of ≥400 ng/mL after 2 weeks predicted for failure in 88% of the cases, whereas levels <400 ng/mL predicted for success in 72% of the cases. However, the specific cutpoint of 400 ng/mL cannot be extrapolated to other patients because it depends so much on the previous transfusion history.

In a subset of patients from a large multicenter study, some prediction of response could be derived from changes observed in reticulocytes and Hb from baseline to week 2 of therapy (Abels 1992; Henry et al. 1995) (Fig. 6). Among patients not receiving chemotherapy (Fig. 6A), the response rate was poor when the 2-week increment of Hb level was <0.5 g/dL, but it was excellent when the Hb level or reticulocyte count increased by ≥0.5 g/dL or ≥40,000/μL, respectively. The predictive power of these parameters was much less substantial when the hemoglobin increased by ≥0.5 g/dL but the reticulocyte elevation was smaller. Adequate prediction of response could not be provided on the basis of Hb and reticulocyte changes in patients receiving concomitant chemotherapy (Fig. 6B). Although some improvement in forecast could be obtained in patients increasing their Hb by ≥1 g/dL after 4 weeks of treatment, predicting response on the basis of the response itself may appear to be trivial.

Predictive algorithms based on a combination of baseline parameters and early changes

A combination of baseline parameters and early changes observed after 2 weeks of rhEPO may provide another useful approach. Among evaluable

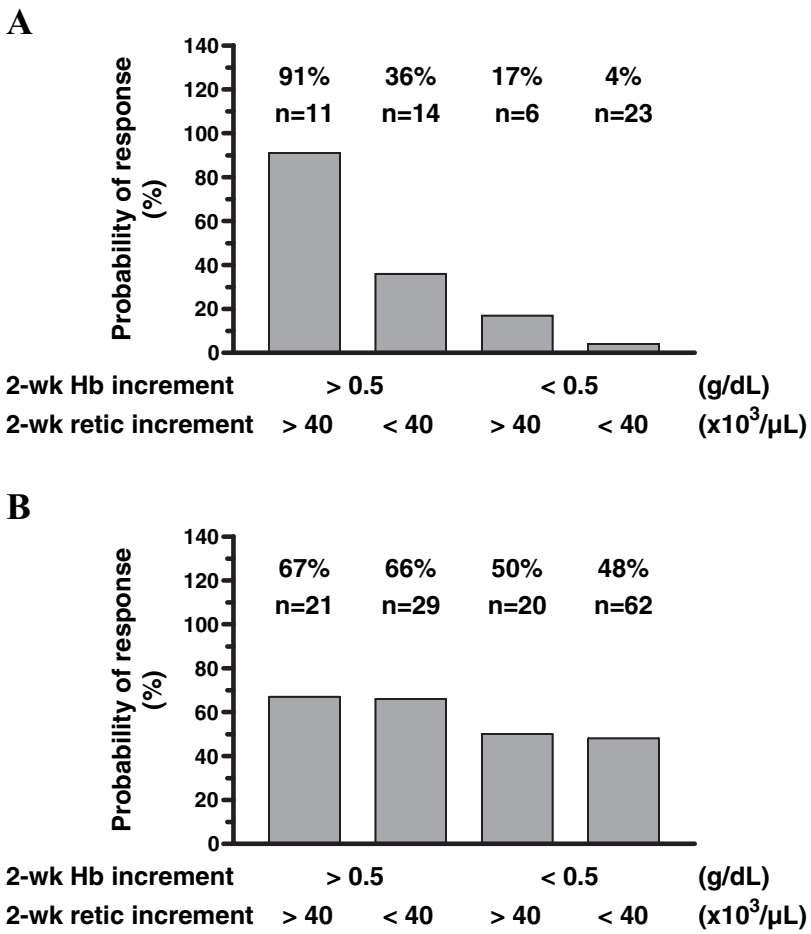

Fig. 6. Prediction of response to EPO in the anemia of cancer by the 2-wk Hb and reticulocyte increments (Henry et al. 1995). A good prediction can be obtained in patients not receiving chemotherapy (**A**) but not in those receiving chemotherapy (**B**)

patients treated in a large multicenter study, the failure rate was almost 90% when baseline serum O/P Epo was higher than 0.9 or when serum O/P Epo was less than 0.9 but the Hb increment by week 2 was <0.3 g/dL (Cazzola et al. 1995) (Fig. 7). On the other hand, the success rate was around 90% when baseline serum O/P Epo was less than 0.9 and Hb increased by ≥0.3 g/d. Similar findings were obtained in a smaller study in children with solid tumors: an O/P ratio <1.0 at baseline and an Hb increment >0.5 gr/dL after 2 weeks were associated with higher response rates (Leon et al. 1998). In another large single center study, the combined use of baseline serum EPO and the 2-week increment of sTfR proved to be very powerful (Cazzola et al. 1996) (Fig. 8). Only 18% of patients with a baseline serum EPO greater

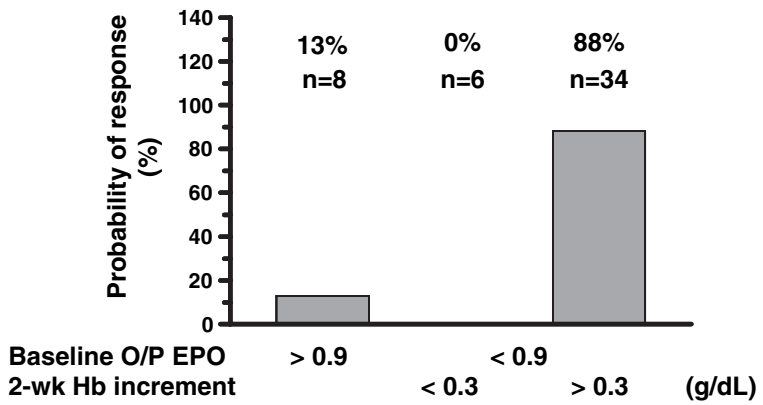

Fig. 7. Prediction of response to rhEPO in the anemia associated with lymphoma or multiple myeloma by the baseline observed/predicted serum EPO ratio and the 2-wk Hb increment (Cazzola et al. 1995)

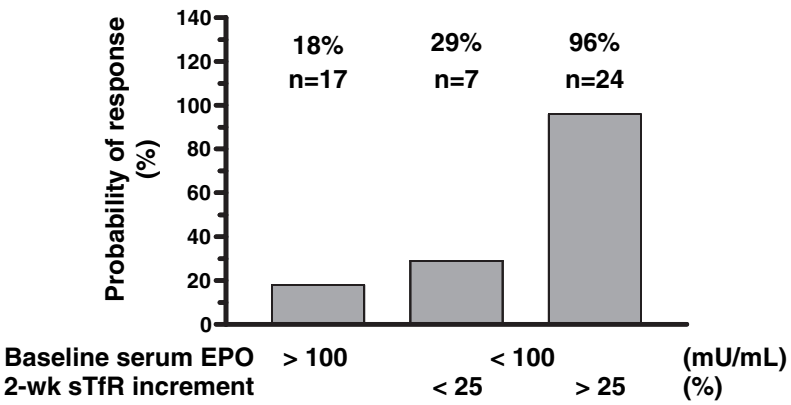

Fig. 8. Prediction of response to rhEPO in the anemia of cancer by the baseline serum EPO level and the 2-wk sTfR increment (Cazzola, 1996 18252 /id)

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 a large series of patients combined from four different randomized trials, increase in Hb and reticulocytes as well as lower absolute values for ferritin and/or transferrin saturation after 2–4 wks were all associated with higher response rates to rhEPO (Littlewood et al. 2003). In this study, two-factor analysis, combining Hb increment after 4 wks >1 g/dL with either baseline EPO <100 U/L or ferritin <400 ng/mL or transferrin saturation <40%, yielded response rates of about 90% in the good vs 45% in the poor prognostic groups, respectively.

Three-factor analysis did not add any specificity or sensitivity to the predictive algorithm.

Applicability of predictive factors

There are a number of theoretical reasons why some or all of these parameters could not be of value in certain situations. 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 rhEPO therapy is to prevent an anemia that is not yet present, in those in whom better tumor oxygenation before radiotherapy is sought, or in disorders characterized by universal EPO deficiency. Even among cancer patients, whereas low baseline serum EPO levels or decreased observed-to-predicted EPO levels (O/P ratio) were associated with a significantly higher probability of response in patients with hematologic malignancies, this was usually not the case in patients with solid tumors. On the other hand, Hb increments after 2 weeks of treatment may be of value in steady state patients, but are of little help in transfused patients and in those in whom rhEPO is intended to prevent the occurrence of severe anemia but cannot avert some decrease in Hb induced by phlebotomy or myelosuppressive treatments. Finally, changes in parameters directly reflecting erythropoietic activity, i.e. reticulocyte counts and sTfR, may be the most appropriate. However, changes in reticulocyte counts may simply reflect output of shift reticulocytes and not true expansion of erythropoiesis, and often have not been found to be a good indicator of response (Beguin et al. 1993b; Ludwig et al. 1994). Although sTfR levels represent the best quantitative measurement of total erythropoietic activity, they may also increase secondary to functional ID (Huebers et al. 1990). In addition, particularly in patients treated with chemotherapy, the timing of the evaluation of these parameters relative to chemotherapy may be critical for their interpretation. For instance, measuring serum EPO after chemotherapy may yield elevated levels compared to pre-chemotherapy values, without any change in Hct (Beguin et al. 1991) (Fig. 4). Finally, the most effective predictive algorithm may also vary according to the dose of rhEPO used (Cazzola et al. 1995). For instance, front-loading regimens with high doses of rhEPO may well yield significantly faster responses (Glaspy et al. 2003), which in turn could prove more useful to identify poor responders earlier, allowing physicians to decide to stop treatment after 2–4 wks when no evidence of stimulated erythropoiesis is detected.

Myelodysplastic syndromes (MDS)

The response rate to rhEPO therapy is much less in MDS patients compared to patients with other forms of cancer (Hellstrom-Lindberg 2003, see chapter

Table 4. Prediction of good response to rhEPO in MDS

- Treatment with rhEPO alone:
  - Transfusion-independence
  - Serum EPO <200 mU/mL
  - RA or RAEB I
- Treatment with rhEPO + rhG-CSF:
  - Transfusion needs <2 U/mo
  - Serum EPO <500 mU/mL
  - RA or RAEB I or RA-S

20). Hence, it would be even more critical to identify possible predictive factors of response in this particular patient population (Table 4). These patients can be treated with rhEPO alone or in combination with low-dose recombinant human granulocyte colony-stimulating factor (rhG-CSF). Although no study has compared the two approaches, the combination of rhEPO and rhG-CSF may be associated with better response rates (40–50%) compared to treatment with rhEPO alone (20–25%) (Hellstrom-Lindberg 2003, see chapter 20). Moreover, the addition of rhG-CSF has been associated with response in rhEPO-resistant patients, while rhG-CSF withdrawal has caused loss of response.

In series of patients treated with rhEPO alone, age (Stein et al. 1991; Rose et al. 1995; Stasi et al. 1997a; Terpos et al. 2002), gender (Stein et al. 1991; Rose et al. 1995; Stasi et al. 1997a; Terpos et al. 2002), type of MDS (Stein et al. 1991), cytogenetics (Stasi et al. 1997a), time since diagnosis (Stein et al. 1991; Rose et al. 1995; Stasi et al. 1997a; Terpos et al. 2002), time since initiation of transfusions (Stein et al. 1991), transfusion requirements (Rose et al. 1995; Stasi et al. 1997a; Terpos et al. 2002; Terpos et al. 2002) or baseline Hct/Hb (Rose et al. 1995; Stasi et al. 1997a; Terpos et al. 2002), reticulocytes (Stasi et al. 1997a; Terpos et al. 2002), platelets (Terpos et al. 2002) or neutrophils (Terpos et al. 2002) have usually not been found to be associated with response. Others have obtained better responses in patients with refractory anemia (RA) compared to those with RA with ring sideroblasts (RAS) (Rose et al. 1995; ICSG 1998; Terpos et al. 2002) or RA with excess of blasts (RAEB) (Rose et al. 1995; ICSG 1998; Terpos et al. 2002; Wallvik et al. 2002), particularly those with RAEB-II (Terpos et al. 2002), patients with normal cytogenetics (Terpos et al. 2002; Wallvik et al. 2002) or no need for transfusions (Wallvik et al. 2002). Although some small series have not found baseline serum EPO levels to be useful predictors of response (Stein et al. 1991; Stasi et al. 1997b), most studies have found that responders had lower serum EPO levels at baseline compared to nonresponders (Depaoli et al. 1993; Rose et al. 1995; Stasi et al. 1997a; ICSG 1998; Terpos et al. 2002; Wallvik et al. 2002). Cutoff values of 50 (Wallvik et al. 2002), 100 (Rose

et al. 1995), 150 mU/mL (Terpos et al. 2002), or 200 mU/mL (Hellstrom-Lindberg 1995; ICSG 1998) have been identified as the most significant, although the use of the O/P ratio could improve separation into responders and nonresponders (Musto et al. 1995). Increased erythroid cellularity in bone marrow or elevated BFU-E in peripheral blood were also found to be highly predictive of response (Stasi et al. 1997a). Erythroid responses were mostly obtained in patients with the glutathione S-transferase (GST) M_1 null genotype and not the GST T_1 null genotype (Tsabouri et al. 2004). Poor responders have been found to have higher serum TNF-α levels with (Musto et al. 1994a) or without (Stasi et al. 1997b) elevated IL-1 levels compared to responders. Responders may be characterized by sTfR levels inadequately low for the degree of anemia (Musto et al. 1994a), but such evidence of intrinsic marrow hypoproliferation is not predictive of response to rhEPO (Bucalossi et al. 1996; Hellstrom-Lindberg et al. 1998). Soluble TfR levels have been shown to increase in response to rhEPO, but early elevation of sTfR levels may overly predict later Hb response because in some patients this may only represent stimulation of ineffective erythropoiesis (Adamson et al. 1992; Cazzola et al. 1992; Ghio et al. 1993; Musto et al. 1994b). Although nonresponders usually do not show modifications while responders increase sTfR levels (Musto et al. 1994b; Hellstrom-Lindberg et al. 1998; ICSG 1998), patients with increased sTfR without concomitant elevation of high fluorescence reticulocytes also do not show significant Hb response (Musto et al. 1994b). An early meta-analysis of 205 patients from 17 studies identified RAS vs other types of MDS, transfusion-dependence vs no need for transfusion, and serum EPO levels above 200 mU/mL vs lower levels, as predictors of poor response to rhEPO (Hellstrom-Lindberg 1995, see chapter 20) (Table 4). Patients with no transfusion requirements and MDS other than RAS had a response rate ≥50%, irrespective of their serum EPO levels. Patients with RAS had a 33% response rate when serum EPO was <200 mU/mL, but the others (RAS with transfusion needs or serum EPO >200 mU/mL, MDS other than RAS with transfusion needs and serum EPO >200 mU/mL showed response rates lower than 10%. It should be emphasized that prolonged duration of treatment may be associated with improved response rates (Terpos et al. 2002).

Most reports of patients treated with a combination of rhEPO and rhG-CSF have also failed to identify age (Negrin et al. 1993; Negrin et al. 1996; Mantovani et al. 2000), gender (Remacha et al. 1999; Mantovani et al. 2000; Hellstrom-Lindberg et al. 2003), type of MDS (Negrin et al. 1993; Negrin et al. 1996; Hellstrom-Lindberg et al. 1997; Remacha et al. 1999; Mantovani et al. 2000; Hellstrom-Lindberg et al. 2003), time since diagnosis (Negrin et al. 1993; Negrin et al. 1996; Hellstrom-Lindberg et al. 1997; Remacha et al. 1999; Mantovani et al. 2000), prior transfusion requirements (Negrin et al. 1993; Negrin et al. 1996; Mantovani et al. 2000), bone marrow erythroid cellularity (Negrin et al. 1996; Hellstrom-Lindberg et al. 1997), IPSS score

(Hellstrom-Lindberg et al. 2003), baseline neutrophils (Negrin et al. 1993; Negrin et al. 1996; Hellstrom-Lindberg et al. 1997; Mantovani et al. 2000), platelets (Negrin et al. 1993; Negrin et al. 1996; Remacha et al. 1999; Mantovani et al. 2000) or reticulocytes (Negrin et al. 1993; Mantovani et al. 2000) as predictors of response. However, higher reticulocytes (Negrin et al. 1996), Hb (Mantovani et al. 2000), platelets (Hellstrom-Lindberg et al. 1997) or neutrophils (Remacha et al. 1999), as well as transfusion needs (Remacha et al. 1999; Hellstrom-Lindberg et al. 2003), have been found predictive in some studies. Favorable cytogenetics have sometimes (Negrin et al. 1996), but not always (Negrin et al. 1993; Hellstrom-Lindberg et al. 2003), been associated with better responses. The limited experience in RAEB-T and CMML has been very disappointing. Again patients responding well had lower serum EPO levels prior to initiation of rhEPO therapy (Vannucchi et al. 1993; Negrin et al. 1996; Hellstrom-Lindberg et al. 1997; Mantovani et al. 2000; Hellstrom-Lindberg et al. 2003), and cutoff values of 100 mU/mL (Hellstrom-Lindberg et al. 1997), 250 mU/mL (Mantovani et al. 2000) or 500 mU/mL (Negrin et al. 1996; Hellstrom-Lindberg et al. 1997) offered the best discriminative power. Few studies have tested the combination of rhEPO and rh granulocyte/macrophage (GM)-CSF, but only in small groups of patients. Only lower serum EPO (Thompson et al. 2000), higher erythroid cellularity (Stasi et al. 1999) and lower serum TNF-α levels (Stasi et al. 1999) were found associated with better response. No predictor of response was identified in a small series of patients treated with rhEPO and all transretinoic acid (ATRA) (Stasi et al. 2002). In an analysis of patients included in previous American and Scandinavian studies (Hellstrom-Lindberg et al. 1997), a predictive model based on serum EPO levels and transfusion requirements was proposed (Table 4). Using baseline serum EPO as a ternary variable (<100 mU/mL = score +2; 100–500 mU/mL = score +1; >500 mU/mL = score –3) and transfusion needs as a binary variable (<2 U/month = score +2; ≥2 U/month = score –2), three groups were separated: one group (score > +1) with a high probability of response (74%), one (score ±1) intermediate group (23%) and one group (score < –1) with poor response (7%). This model was later validated in other series of patients (Remacha et al. 1999; Hellstrom-Lindberg et al. 2003), but others obtained similar response rates in patients with scores > +1 or ±1 (Mantovani et al. 2000).

Conclusion

Several algorithms have been proposed for patients with the anemia of cancer. Their sensitivity (how well the algorithm identifies all those who will respond) and specificity (how well the algorithm excludes all those who will fail), and thus their overall efficacy, vary considerably. In the study conducted by Ludwig (Ludwig et al. 1994), when one tries primarily to identify

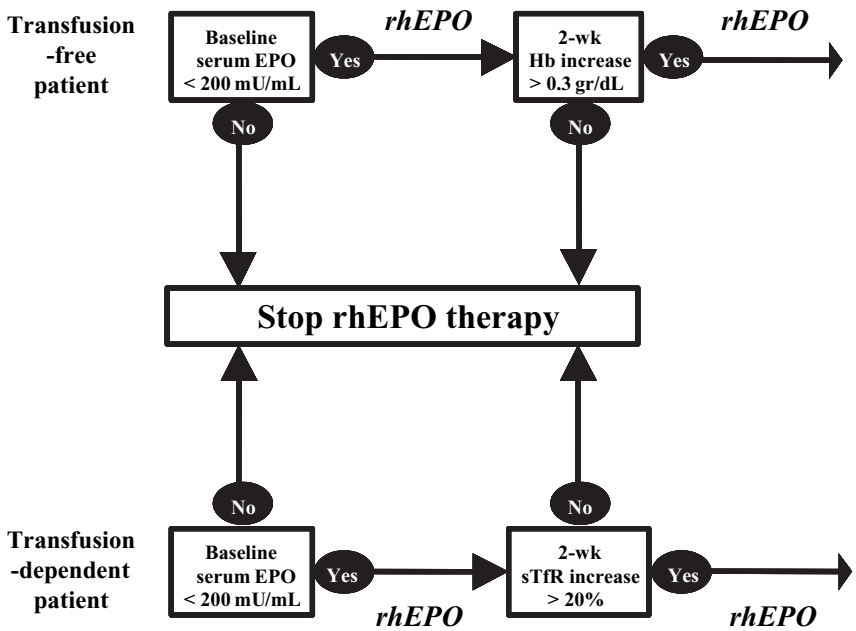

Fig. 9. Practical use of algorithms for prediction of response in cancer patients treated with rhEPO, based on baseline endogenous EPO level and an early (2-wk) indicator of increased erythropoietic activity. The first step (baseline Epo) could be omitted in solid tumor patients. The only difference between untransfused and transfused patients is that the 2-wk Hb increment cannot be used in transfusion-dependent patients and must be replaced by the 2-wk sTfR increment

nonresponders instead of responders, sensitivity and overall accuracy can be increased from 42% and 70% to 76% and 86%, respectively. Overall accuracy is not improved by doing so in the study conducted by Henry in patients receiving chemotherapy, because enhanced sensitivity (54%) is compensated by diminished specificity (52%). The positive predictive value (probability of response in those predicted to respond) of the algorithms is usually better then their negative predictive value (probability of failure in those predicted to fail). 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 Hb or sTfR).

The following attitude can be proposed in practice (Fig. 9):

(1) 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.

(2) Erythropoietic response should be assessed after 2 weeks:
   – In untransfused patients, if the Hb has increased by at least 0.3–0.5 g/dL, continue treatment; otherwise stop treatment or consider doubling the dose (although there is no published evidence that this will work (Bokemeyer et al. 2004)) and definitively discontinue EPO after 2 additional weeks if Hb has not increased by at least 0.3 g/dL.
   – In transfused patients, if sTfR has increased by at least 20%, continue treatment; otherwise stop treatment or consider doubling the dose (although there is no published evidence that this will work (Bokemeyer et al. 2004)) and definitively discontinue rhEPO after 2 additional weeks if sTfR has not increased by at least 20%.

(3) It is critical that all preventable causes of failure are identified prospectively and corrected, or else no predictive model will be valid. In particular this includes vigorous iron supply and energetic treatment of intercurrent complications such as infections and bleeding.

(4) MDS patients could be treated with rhEPO alone when they have RA or RAEB with serum EPO <200 mU/mL and no transfusion need, or with a combination of rhEPO and rhG-CSF if they have RA, RAS or RAEB with serum EPO <500 mU/mL and transfusion needs lower than 2 U/month (Hellstrom-Lindberg 2003, see also chapter 20) (Table 4). Failure to detect increases in sTfR after 2 weeks should justify discontinuation of rhEPO therapy.

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