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Red Cell Survival in Relation to Changes in the Hematocrit: More Important than You Think

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Key Words
Dialysis · Chronic renal failure · Erythropoietin · Dosing algorithm · Erythrocyte lifespan · Erythrocyte survival function

Abstract
The management of anemia in patients with chronic renal failure has greatly improved with the availability of recombinant human erythropoietin in the late 1980s, leading to a considerable reduction in mortality and morbidity and to an improvement in quality of life. The findings from recent controlled clinical outcome trials have resulted in a rather narrow, generally accepted therapeutic hematocrit target range. However, currently available dosing algorithms do not permit achievement and maintenance of target values within the therapeutic range in many patients. One possible explanation for this failure may be the ignorance of a finite erythrocyte lifespan not integrated into most algorithms. The purpose of this article is to underline the essential role played by the erythrocyte lifespan in the erythropoietic response to recombinant human erythropoietin and to encourage the integration of this concept in the future development of computer-assisted decision support systems.

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Introduction

Relative endogenous erythropoietin deficiency secondary to chronic renal failure is generally evident when the glomerular filtration rate (GFR) decreases below 30 ml/min but may be observed as early as the GFR decreases below 60 ml/min. Chronic anemia is evident in more than 90% of patients undergoing dialysis therapy [1]. Untreated severe anemia in end-stage renal disease patients is associated with a high cardio- and cerebrovascular mortality and morbidity, loss of cognitive and mental function, chronic fatigue and an impaired quality of life [2–6]. With the availability of recombinant human erythropoietin (rHuEPO) in the late 1980s, the situation has changed considerably, allowing a significant correction of renal anemia without transfusion requirements in the majority of patients today [7].

Despite 20 years of experience with rHuEPO therapy, there are still considerable discrepancies between EPO treatment recommendations and clinical practice [8]. This fact is at least partly explained by the peculiar pharmacodynamic properties of rHuEPO, making its use difficult even in hands of experienced nephrologists. Three major problems are encountered when prescribing an adequate rHuEPO dose. First, there is high inter- and intraindividual response variability owing to numerous clinical and biological parameters affecting the dose-response relationship. Second, the individual dose-response relationship is generally not linear, and third, the biological

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effect of rHuEPO lags behind and persists beyond dose changes due to the long lifespan of mature erythrocytes. These problems are well known and have been studied in several research trials [9–12]. Nevertheless, while the necessity to systematically monitor hemoglobin and/or hematocrit levels during therapy with rHuEPO is generally accepted, no transition from research findings to clinically useable rHuEPO dosage algorithms has so far taken place.

There is increasing evidence of a rather narrow optimal therapeutic hemoglobin concentration range from 11 to 12 g/dl during treatment with rHuEPO in patients with chronic kidney disease [13, 14]. Overshooting of the target hemoglobin concentration is often observed at the beginning of the rHuEPO substitution and in situations of perturbed steady state and is associated with an increased rate of serious complications such as vascular access failure, thrombosis and/or exacerbated arterial hypertension. The latter in combination with increased vascular resistance and decreased rheologic properties noted in 40% of patients with increased hemoglobin levels, may lead to the development of adverse cardiovascular events [15–17]. Furthermore, bearing in mind the high direct and indirect economic costs of rHuEPO, achievement of stable hemoglobin and hematocrit levels within the optimal range with fewer fluctuations and less frequent laboratory checks might result in considerable clinical improvement, as well as economic and resource savings.

It is striking that, despite all the medical and economical pressure to reach and stay within a hematocrit target range, currently available tools to guide rHuEPO dosing in renal failure are mostly sparse or even flawed. Dose recommendations to initiate a therapy with rHuEPO usually describe 2 sequential treatment phases, a 'correction phase' and a 'maintenance phase'. The scope of this article is to show that such approaches are not based on biological principles and that true comprehension of the pharmacodynamic determinants of erythropoiesis will help to prevent erroneous decisions with respect to dosing of rHuEPO.

Pharmacodynamics of Erythropoiesis

Pharmacokinetics, i.e. the distribution and elimination of different application forms of rHuEPO and other erythropoiesis-stimulating agents, are not discussed in this article. The 2 major pharmacodynamic determinants of erythropoiesis are the transductional response of proliferating precursor cells of the erythroid line to rHuEPO and the erythrocyte lifespan. Several theoretical pharmacodynamic models describing the hematological response to rHuEPO treatment have been developed during the last decade. Generally, these models are based on catenary, precursor-dependent indirect response models with cell lifespan concept [10, 11, 18–23]. The mechanistic nature of these models allows the assessment of dynamic changes of red blood cells (RBCs) and precursor cells during rHuEPO treatment including intercompartmental differentiated kinetics and retroinhibition, but their mathematical complexity and their lack of robustness due to complex parametric estimation have so far precluded their use in clinical settings.

rHuEPO Dose-Response Relationship

It is well known and we have shown in a population pharmacodynamic study that there is a large intra- and interindividual variability in the dose-response relationship with rHuEPO [11]. Furthermore, the individual dose-response relationship is not linear but becomes rather flat in the higher dose range. Several observations may at least partly be attributed to this nonlinear dose-response relationship. The mean consumption of rHuEPO varies considerably between dialysis units and this is not necessarily reflected in different mean hematocrit levels. Conversion studies from intravenous to subcutaneous rHuEPO or between different erythropoiesis-stimulating agents have shown inconsistent results, possibly dependent on the initial location on the dose-response relationship curve before conversion took place [24, 25]. Furthermore, it is currently debated if the rHuEPO dose should be decreased or rather stopped if the erythropoietic response is in a range where an overshooting of the hematocrit over the target range might be expected. As can easily be learned from figure 1, a 50% dose reduction will result in a significant decrease in RBC production rate in the lower dose range, while only a minimal effect of a 50% dose reduction is expected in the higher dose range. With no prior information about the individual dose-response relationship between rHuEPO and the RBC production rate, we strongly advice to withhold rHuEPO whenever an overshooting above target levels must be expected and to recommence rHuEPO at a lower dose only when the hematocrit starts falling again.

RBC Lifespan

RBCs might be eliminated from the circulation unexpectedly, e.g. by bleeding, or they might reach their natural lifespan and die from old age. In the first case, the probability of death is the same for all erythrocytes, in-

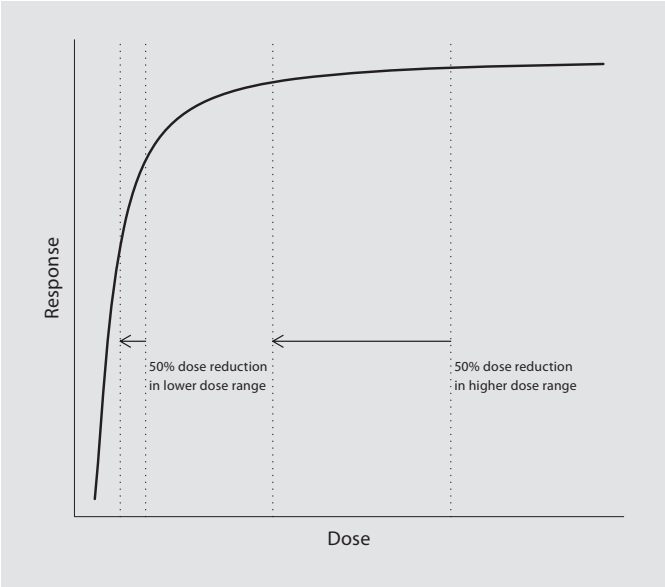

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Fig. 1. Relationship between rHuEPO dose and erythropoietic response (Hill function). A 50% dose reduction in the higher dose range has a negligible effect on the erythropoietic response whereas the same procedure in the lower range leads to a significant decrease in RBC production.

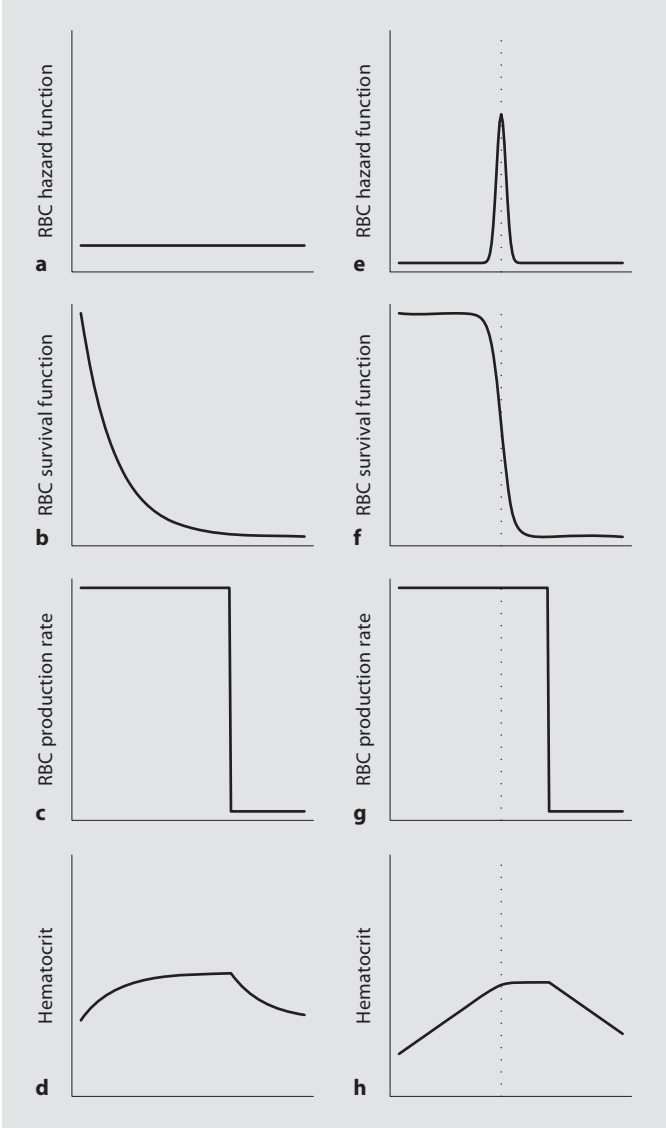

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Fig. 2. Schematic presentation of 2 different conceptual approaches describing the time course of RBCs. **a–d** The probability of an RBC to be destroyed is time independent and constant (**a**), i.e. random destruction. Due to the constant hazard (**a**), there is no need to know anything about the history of the RBC to determine its fate (system without a memory). The resulting survival function is exponential (**b**). **e–h** In this probabilistic approach, the notion of the RBC mean lifespan (dashed lines) and width of distribution about the mean lifespan are introduced (**e**). Integrating **e** yields a sigmoid survival function (**f**) showing that RBC survive as long as they have not reached their finite lifespan. This system needs a memory to keep track of the RBC until it reaches its finite lifespan.

dependent of age. Furthermore, the hazard, i.e. the probability of instant death, remains constant throughout the life of an erythrocyte. Figure 2a–d shows the hazard function, survival function and the expected change in hematocrit for a given RBC production rate that is suddenly stopped.

Figure 2e–h shows the same parameters when erythrocytes die from old age only. The hazard remains 0 until the natural lifespan is reached and then suddenly rises. The corresponding survival function is 1 until the lifespan is reached and then drops to 0. Note that for a given production rate a steady state is reached independent of the way RBCs are eliminated – by ageing and/or random destruction.

In healthy adults, the erythrocyte lifespan is about 120 days and shows a narrow width of distribution, i.e. all erythrocytes of the same age die within a few days [26]. The RBC lifespan is markedly reduced in some patients with renal failure [27]. We have previously calculated a mean RBC lifespan of 64 days in dialysis patients with an inter- and intraindividual variability of 34 and 5%, respectively [11]. The interindividual variability is high, but the intraindividual variability is similar to the one observed in healthy subjects. Considering that all produced erythrocytes will survive a certain amount of time (corresponding to one erythrocyte lifespan) before being removed from the circulation, the erythron of a chronic renal failure patient under constant rHuEPO substitution in steady

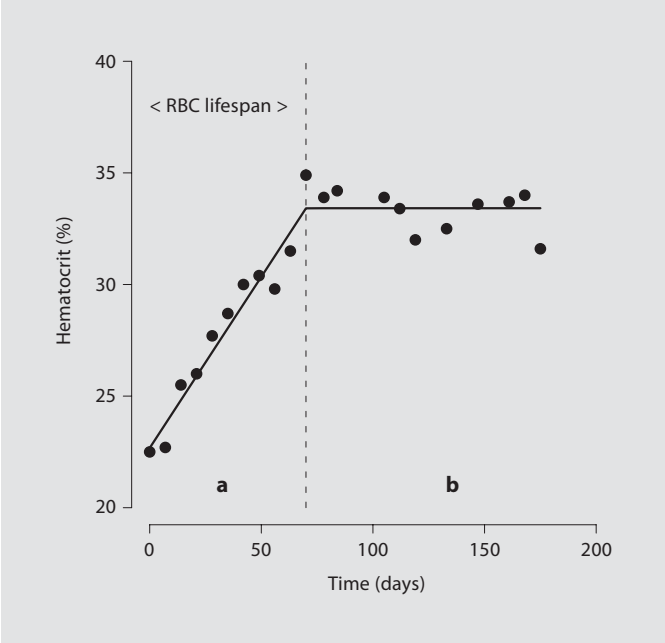

Fig. 3. Hematocrit values in a patient treated with a constant rHuEPO dose. **a** rHuEPO causes an increase in RBC production rate. Hematocrit increases because none of the newly produced erythrocytes die at this early stage. **b** After reaching 1 RBC lifespan, erythrocytes die at the current production rate. A new steady state is reached at a higher hematocrit.

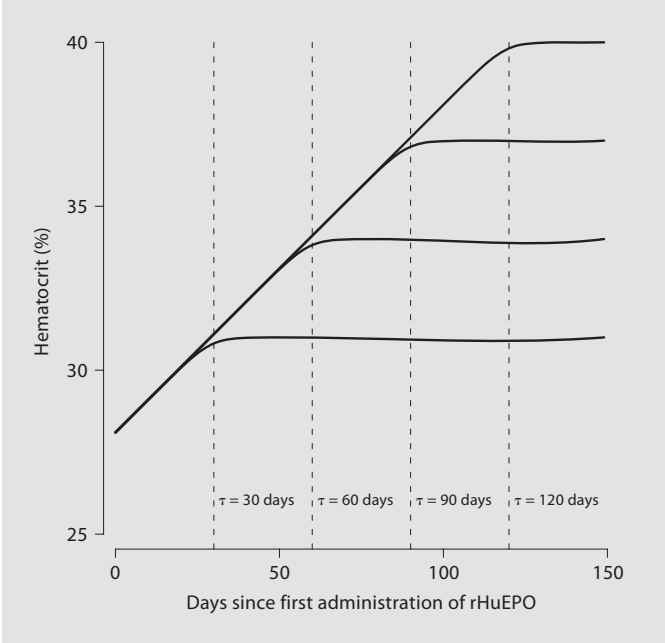

Fig. 4. Theoretical course of hematocrit values in a patient treated with a constant rHuEPO dose assuming different RBC lifespans τ (30, 60, 90 and 120 days respectively; dashed lines). For a given RBC production rate, the RBC lifespan not only determines the time needed to achieve a new steady state, but also the extent of the increase in hematocrit.

state will consist of a uniformly distributed population of erythrocytes ranging in age from recently produced to senescent erythrocytes. Every day, senescent erythrocytes will be replaced by the same number of new cells.

If the rHuEPO dose is increased, additional erythrocytes will be produced and the total number of erythrocytes will steadily augment until the first of these newly produced erythrocytes start dying, i.e. after a period corresponding to the lifespan of these erythrocytes. Thereafter, a new steady state will be achieved and, as long as the rHuEPO dose does not change, the erythrocyte count will remain constant (fig. 3). Thus, the lifespan of the erythrocytes will determine the time needed to achieve a new steady state. Furthermore, both the lifespan and transductional response of precursor cells to rHuEPO will determine the extent of the final hemotocrit changes (fig. 4).

Considering these particular pharmacodynamic properties, the concept of distinguishing between a 'correction phase' and a 'maintenance phase' becomes anything but rational. Ignoring the long lifespan of the erythrocytes and the resulting response lag beyond dose changes may lead to oscillations or overshooting when current dosing recommendations are applied (fig. 5). Furthermore, all available dosing algorithms, conventional [28, 29] or based on artificial neural networks [30], will eventually fail if they do not take into account all information that dates back at least one RBC lifespan.

EPO Treatment Algorithms

Based on the concepts mentioned above and assuming that a sufficient iron supply is ensured, the expected effect of a rHuEPO therapy on hematocrit levels can be described by the following general model [11]:

$$Hct(t) = Hct_0 + \sum_{i=1}^{n} \theta(t - T_i)(\beta_i - \beta_{i-1}) \int_0^{t-T_i} S(x)\,dx$$

$$\theta(x) = \begin{cases} 1 & if \quad x \geq 0 \\ 0 & if \quad x < 0 \end{cases}$$

where $Hct(t)$ is the hematocrit at time t, Hct_0 is the baseline hematocrit, T_i are the timepoints of rHuEPO dose adaptions, β_i are the RBC production rates induced by

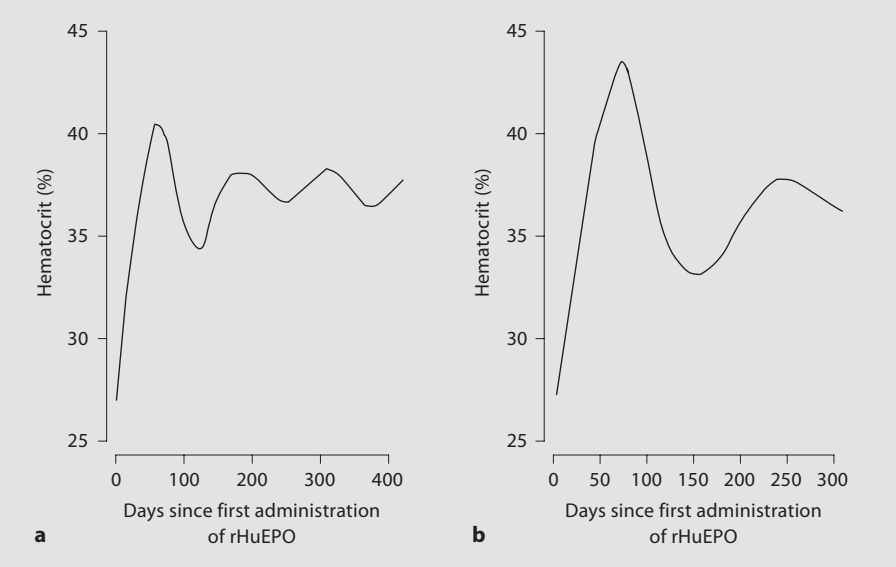

Fig. 5. Simulated hematocrit values in a patient starting with rHuEPO substitution according to current guidelines. **a** Ignoring the long lifespan of RBCs may lead to oscillations if frequent dose adaptations are performed and a steady state is never reached. **b** Overshooting of the target hematocrit level may be observed despite the recommended rHuEPO dose reduction. This may happen mainly in the higher dose range, where the rHuEPO dose-response curve is rather flat (see fig. 1).

these doses, $\theta(x)$ is the step function and $S(x)$ is the RBC survival function.

Any RBC survival function can be used with the model described above. A survival function including concomitant aging of RBC and random destruction can be written as:

$$S(x) = \frac{e^{-kx}}{1 + e^{\alpha(x-\tau)}}$$

where k denotes the random destruction coefficient and α is an empiric value to describe the dispersion of RBC lifespans around a given RBC lifespan τ.

We have previously shown that the RBC lifespan τ can either be determined by estimating the time period from starting rHuEPO or from any dose change to reach steady-state conditions. Once steady-state conditions are reached, the product of the RBC production rate and RBC lifespan τ can no longer be separated. However, if 1 of the 2 parameters is known, the other can easily be estimated. Our current research focuses on the possible estimation of the lifespan τ from the observed decrease in hematocrit when rHuEPO dosing is interrupted for a short time period.

With respect to the RBC production rate, any function describing the induced changes in RBC production rate by rHuEPO can be used in the general model described above. The transductional response of the erythroid line to rHuEPO may be expressed as a linear dose-response relationship (over the whole dose range or for each dose level). If EPO plasma concentrations (C_{EPO}) are known, a more physiological nonlinear model introducing the Hill function may be applied:

$$\beta = k_{in}\left(1 + \frac{E_{max}\, C_{EPO}}{EC_{50} + C_{EPO}}\right)$$

in which k_{in} represents the basal, apparent zero order production rate of precursor cells.

rHuEPO dose changes might result in intercompartmental retroinhibition, prolongation of the apparent lifespan of the precursor cells induced by stress maturation and additional mitosis of the precursor cells with enlargement of their pool. Ignoring these transient dynamic changes, the amount of precursor cells and reticulocytes remains constant in steady state, and the catenary system (precursor cells, reticulocytes and RBCs) is considered to be deterministic (no cell losses). A linear relationship links the lifespan of precursors τ_{Pre} to that of successor cells τ_{Suc}. If the reticulocyte count under basal conditions Co_{Pre}^{SS} and their lifespan τ_{Pre} are known, k_{in} may be estimated:

$$\tau_{Suc} = \frac{Co_{Suc}^{SS}}{Co_{Pre}^{SS}}\,\tau_{Pre}$$

$$k_{in} = \frac{Co_{Pre}^{SS}}{\tau_{Pre}}$$

It is evident that at least one of the lifespans τ_{Pre} or τ_{Suc} has to be known.

Conclusions

Only few clinically useful dosing algorithms and prescription tools are available today. To our knowledge, none of these tools base their dosing recommendations on all the available information over the whole treatment period. Limiting decisions to observations dating back only few days or weeks, and so failing to cover at least the full period of the expected RBC lifespan of 2 to 4 month, will fail to predict correct dose changes in some patients. As described above, theoretical models based on all currently known biologic determinants including finite RBC lifespans do exist but will have to be integrated into the future development of computer-assisted decision support systems.

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