Chapter 9
Anemia Management in the Elderly Dialysis Patient: Is It Different?

Iain C. Macdougall

Introduction

Prior to the 1990s, anemia management in the dialysis patient was fairly limited and was clearly suboptimal. Several strategies were tested and occasionally implemented, including iron supplementation and replacement of other hematinics, such as vitamin B_{12} or folic acid, and the use of androgens (which are weak stimulators of erythropoiesis). Many dialysis patients remained severely anemic and were supported by regular red cell transfusions, which often had to be administered every 2–4 weeks to patients whose baseline hemoglobin concentration was about 5 or 6 g/dL. Transient increases in the hemoglobin concentration to levels of around 10 or 11 g/dL were seen following the blood transfusions, but within a few weeks, the hemoglobin concentration had once again fallen to the baseline level of around 5–6 g/dL. Further transfusions were administered, and this desperate cycle of treatment repeated itself, resulting in transfusional iron overload. Thus, it was not uncommon for dialysis patients to run serum ferritin concentrations in the 1000's. Other complications of blood transfusions included the transmission of infectious agents, particularly viral, as well as transfusion reactions, including transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO). Although rare, such complications could be devastating. Another important complication of blood transfusions includes HLA sensitization, which renders subsequent renal transplantation problematic; although this remains a concern, it is clearly of little relevance to elderly dialysis patients, most of whom are not suitable for kidney transplantation.

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I.C. Macdougall, BSc, MD, FRCP
Department of Renal Medicine, King's College Hospital, London, UK

Renal Unit, King's College Hospital, London SE5 9RS, UK
e-mail: iain.macdougall@nhs.net

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The advent of recombinant human erythropoietin in the late 1980s heralded a logical and much more satisfactory solution to the management of anemia in dialysis patients [1, 2]. For the first time, it was possible to achieve a steady and sustained increase in hemoglobin concentration without transfusional support, and indeed the use of red cell transfusions in hemodialysis patients dramatically decreased during the 1990s. Recombinant human erythropoietin or epoetin, as it became known, was followed by two other erythropoietic agents, namely, darbepoetin alfa and pegylated epoetin beta. The use of these agents increased the demands for iron, and there was renewed focus on iron management.

There are, however, specific aspects of anemia management that are more relevant to the elderly dialysis population. These include many other causes of anemia in the elderly population in general but still relevant for the dialysis patient. The prevalence of hematological conditions, particularly myelodysplastic syndrome, is much increased in the older patient, as are many cancers. Thus, anemia management in the elderly may be somewhat complex, and resistance to ESA and iron therapy is common. Poor diet and nutritional deficiencies are also more common in the elderly. The remainder of this chapter will discuss the prevalence and causes of anemia in the elderly, ESA therapy, iron management, and the role of blood transfusions. Specific attention will be given to the use of ESA therapy in patients with a previous or current history of stroke or malignancy, as well as a discussion on how to manage the patient who is resistant to ESA therapy.

Prevalence of Anemia in the Elderly

The incidence and prevalence of anemia increase with age. Using the World Health Organization definition of anemia (hemoglobin <13 g/dL for men and <12 g/dL for women), 11.0 % of men and 10.2 % of women aged 65 years or older and living in the community were anemic, according to the Third National Health and Nutrition Examination Study (NHANES III) data set [3]. The prevalence of anemia increases sharply in later life to values of 26.1 % in men and 20.1 % in women aged 85 years and over [3].

A high prevalence of anemia was also found in a longitudinal Swedish study of elderly subjects followed at 1–5 year intervals for 18 years [4], as well as a cross-sectional study of community-dwelling older persons in the Chianti area of Italy (CHIANTI Study) [5]. Much higher prevalences of anemia in the elderly dialysis population are seen, with upward of 95 % of patients being anemic or requiring treatment with ESA therapy.

The implications of anemia in the elderly population are severalfold. There are strong associations with a number of unfavorable outcomes that include death, functional dependence, dementia, falls, and cardiovascular disease. There are also economic implications for anemic individuals, with healthcare costs (both direct and indirect) being substantially higher in anemic patients compared to those without anemia.

Causes of Anemia in the Elderly

The major causes of anemia in the elderly, both in nondialysis and dialysis patients, are erythropoietin deficiency and iron deficiency (Table 9.1). Even without chronic kidney disease, elderly patients are known to have inappropriately low levels of erythropoietin for the degree of anemia, and it is estimated that approximately 30 % of anemia in the elderly is due to relative or absolute erythropoietin deficiency [6]. In approximately 50 % of cases, anemia in the elderly is due to reversible causes, including iron, B_{12}, and folate deficiency [6]. Chronic inflammation [6] and blood loss (which may be occult and secondary to malignancy) are also very common in the elderly and may also exacerbate anemia in this age group. There is a direct relationship between the prevalence of myelodysplastic syndrome and aging (clinical clues include a raised mean cell volume (MCV), resistant anemia, and abnormally low white cell and platelet counts). Hematinic deficiencies such as those associated with iron, B_{12}, and folate are easily diagnosed and treated, as is hypothyroidism which often presents with a macrocytic anemia. Gastrointestinal inflammation such as gastritis, esophagitis, and duodenitis, as well as peptic ulceration, may result in occult bleeding from the GI tract. Some drugs may also have anemia as a side effect and exacerbate this condition (Table 9.1).

Iron deficiency is also fairly common in the elderly and particularly so in dialysis patients. This may be due to a combination of both decreased iron intake and increased iron losses (Fig. 9.1), and thus, the dialysis population is often found to be in a state of negative iron balance. Iron absorption from the gut is severely impaired due to hepcidin overactivity as a result of increased inflammation [7], and certain commonly used drugs such as proton pump inhibitors and phosphate binders may bind to iron and impede iron absorption. Tea and certain foodstuffs may also have the same effect. In addition to iron losses caused by occult or overt GI bleeding, there may be iron losses due to blood trapping in the dialyzer, as well as secondary to frequent blood sampling. Use of aspirin as cardiovascular prophylaxis and heparin or other anticoagulants on hemodialysis may exacerbate gastrointestinal blood and iron losses.

Malignancy is much commoner in the elderly, and this may exacerbate anemia both by causing blood loss (e.g., bowel cancer) and by exacerbating chronic

Table 9.1 Causes of anemia in the elderly

Relative erythropoietin deficiency
Iron deficiency
B_{12} and/or folate deficiency
Chronic inflammation
Blood loss
Gastrointestinal inflammation (gastritis, esophagitis, duodenitis)
Malignancy
Myelodysplastic syndrome
Hypothyroidism
Drug side effects

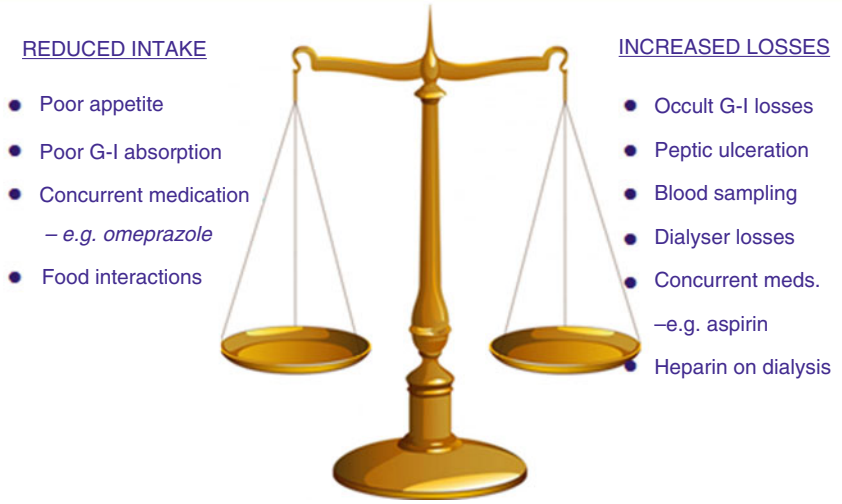

Fig. 9.1 Iron balance in dialysis patients

inflammation (also known as the anemia of chronic disease) [6]. Caution is required in using ESA therapy in patients with current or previous malignancy (see below).

Erythropoiesis-Stimulating Agent (ESA) Therapy

The first-generation ESAs were epoetin alfa and epoetin beta, introduced in the early 1990s. Use of these agents revolutionized the management of anemia in dialysis patients, rendering many individuals free of blood transfusions and causing a sustained increase in the hemoglobin concentration [1, 2]. In hemodialysis patients, epoetin may be administered either intravenously or subcutaneously at a dosing frequency of one to three times per week. In peritoneal dialysis patients, the epoetin is virtually always given subcutaneously.

Subcutaneous administration of epoetin generally results in dose requirements that are 20–30 % lower than those seen with intravenous administration [8].

In 2001, a second-generation ESA was approved for the management of anemia in dialysis patients, called darbepoetin alfa (Aranesp®). The elimination half-life of darbepoetin alfa given intravenously is approximately three times that of epoetin (25.3 h vs 8.5 h). This agent is therefore able to be administered with less frequent injections, usually once per week or once every 2 weeks. In contrast to epoetin, there is no difference in dosing requirements between intravenous and subcutaneous administration with darbepoetin alfa.

A third-generation ESA has also been produced by inserting a polyethylene glycol (PEG) molecule into the epoetin molecule. Pegylated epoetin beta (methoxy polyethylene glycol epoetin beta or CERA; brand name Mircera®) has a much

longer half-life than all the other ESAs, at around 130 h. This allows the agent to be injected once every 2 weeks, or even once a month. Again, there is no difference between intravenous and subcutaneous dosing requirements. For patent reasons, this product has not been able to be marketed in the United States, but it is widely available throughout Europe and the rest of the world. A randomized controlled trial (PATRONUS) showed superiority of pegylated epoetin beta compared to darbepoetin alfa when administered once–monthly to dialysis patients [9].

Most dialysis patients are already on ESA therapy by the time they start dialysis, but not infrequently there are "crash-landers" who present to their nephrologist with end-stage renal failure and often quite severe anemia which requires dialysis and ESA therapy.

Since ESAs were introduced, there has been much debate and controversy about the appropriate target hemoglobin range to aim for in dialysis patients. Following all the early studies which aimed for incomplete correction of anemia, interest then arose in completely normalizing the hemoglobin concentration. A large randomized controlled trial in hemodialysis patients comparing a target hemoglobin of around 14 g/dL with a hemoglobin of around 10 g/dL [10], however, was the first of several studies in the setting of chronic kidney disease to suggest that this strategy of anemia management may be harmful. There was an increased incidence of vascular access thrombosis in the group of patients targeting a normal hemoglobin concentration, and there was also a trend toward a higher risk of reaching the primary endpoint of death or a nonfatal myocardial infarction [9]. Several subsequent studies in nondialysis patients, including CREATE [11], CHOIR [12], and TREAT [13], have also raised concerns about normalization of hemoglobin. The latter study in particular has had the greatest impact on anemia management, and the latest anemia guidelines suggest that subnormal correction of anemia is preferable, with a target hemoglobin of around 10–12 g/dL. In the TREAT Study, aiming for a hemoglobin concentration of around 13 g/dL resulted in a doubling of stroke risk and a more than tenfold increase in cancer-related mortality in patients who had a previous malignancy [13]. Given that stroke and cancer are much more prevalent in the elderly population, this has significant implications for the use of ESA therapy in elderly dialysis patients (discussed in greater detail below).

ESA Therapy and Stroke

The incidence of stroke rises progressively with age, and thus, this devastating cardiovascular event is very much more common in the elderly patient. There are real concerns that ESA therapy may exacerbate the risk of stroke if a hemoglobin target of around 13 or 14 g/dL is implemented, and two randomized controlled trials have provided evidence to that effect.

The first trial was in hemodialysis patients recruited from across Europe and Canada [14]. Although the absolute number of strokes in the trial was low, there were nevertheless 12 strokes seen in the group of patients targeting a higher hemo-

globin concentration of over 13 g/dL, compared to only four strokes in the group of patients targeting a hemoglobin concentration of around 10 g/dL ($p = 0.045$) [14]. The TREAT Study of over 4000 patients with diabetes and nondialysis chronic kidney disease [13] showed a doubling of stroke risk in the group of patients targeting a hemoglobin of 13 g/dL, compared with the placebo group who maintained hemoglobin concentrations of just above 9 g/dL. Overall 154 of the 4038 patients included in this study had a stroke, with 101/2012 (5.0 %) in the active arm and 53/2026 (2.6 %) in the placebo arm (hazard ratio 1.9; 95 % confidence interval 1.4–2.7) [13].

The data from the TREAT Study were subjected to a further detailed analysis to see if any baseline variables could account for the development of stroke in the study population. A multivariate logistic regression model was used to identify baseline predictors of stroke. A number of other factors, including post-randomization blood pressure, hemoglobin level, platelet count, or treatment dose, were also assessed using a nested case-control analysis (1:10 matching) identifying non-stroke controls with propensity matching to see if any of these factors could account for the increased risk related to ESA therapy [15]. None of the baseline variables or any of the factors in the case-control analysis could be used to mitigate the risk of ESA-related stroke. Although the absolute risk of stroke was greater if there was a history of previous stroke, the relative risk of stroke in patients treated with ESA therapy remained at 2:1 versus placebo [15].

It is still not clear why ESA therapy might exacerbate stroke, but it is clear ESAs produce circulating erythropoietin levels that are considerably higher than physiological levels and that there are pleiotropic effects of these agents [16]. Thus, the increased risk of stroke may not be due simply to a higher hemoglobin concentration but to some of the secondary effects of ESA therapy, perhaps their effect on endothelial and platelet function.

The implications of all of this for anemia management are that physicians using ESA therapy should be aware of the potential for exacerbating stroke and in any patients believed to be high risk, the benefits versus the risks of using this treatment should be weighed up carefully. If ESA therapy is used, target hemoglobin concentrations should not exceed 11.5 or 12 g/dL in order to reduce the risk of this potentially devastating adverse effect.

ESA Therapy and Malignancy

Since the introduction of ESA therapy, there have been increasing concerns about the use of this treatment in patients with a history of previous or current cancer. The main concerns center around three main areas, namely, an increased risk of venous thromboembolism and whether there is any increased risk of death or tumor progression.

Most of the oncology trials using ESA therapy showed that targeting hemoglobin concentrations greater than 12 g/dL doubles the risk of venous thromboembolism. This complication is already increased in patients with cancer but appears to be

further exacerbated by ESA therapy. In the CKD setting, in noncancer patients, the only trial that has been large enough to systematically look at the risk of this complication has been the TREAT Study, where again a doubling of the rate of venous thromboembolism was seen [13]. Again, this may be due to the pleiotropic effects of ESA therapy on endothelial and platelet function [16], but the consistency across all the oncology studies in various different types of cancer is harder to ignore.

The mortality risk in patients with malignancy is somewhat less clear. One of the earliest oncology trials of erythropoietin therapy for anemia associated with head and neck cancer suggested that patients whose tumor tissue tested positive for the erythropoietin receptor had a worse survival form those who were negative for the erythropoietin receptor [17]. This work has, however, since been discredited.

However, the publication of the TREAT Study once again raised concerns about the possibility of ESA therapy exacerbating cancer-related death. Patients with active malignancy were excluded from this study, although those who had a previous malignancy from at least 5 years ago and were deemed to be cured could be recruited. In this latter subgroup of patients, analysis of the rate of cancer-related death was conducted, and there was a more than tenfold increase in ESA-treated patients compared to the placebo group [13]. Given that this was not the primary objective of the study, the result needs to be interpreted with caution, although the magnitude of this effect is hard to ignore.

The question of whether ESA therapy can exacerbate the growth of a malignant cell clone is even more controversial. While the main function of erythropoietin is as a growth factor for red cells, there has been much discussion as to whether ESA therapy can also enhance tumor cell growth. This issue is still undecided.

All of the above has resulted in the physician not knowing what to do when a dialysis patient develops cancer. Given the uncertainty, it is perhaps sensible to use the lowest dose of ESA therapy possible, although these are the very patients who often show the greatest resistance to ESAs. Repeated dose escalation should therefore be avoided, and it may have to be accepted that patients on dialysis with an active cancer require red cell transfusional support. If ESA therapy is used, efforts should again be made not to target hemoglobin concentrations above 12 g/dL.

Hyporesponsiveness to ESA Therapy

There are two types of poor response to ESAs. The first is a failure to show a significant increment in hemoglobin concentration, despite repeated increases in ESA doses. The second is characterized by a loss of response to treatment, again despite increased ESA doses. The latter is more common in dialysis patients, although the former may occur in “crash-lander” patients who present with end-stage renal failure with no previous nephrological input. Hyporesponsiveness to ESA therapy should be subjected to a careful and systematic approach, and a cause for this should be rigorously sought. Common causes include iron insufficiency, infection or inflammation, and under-dialysis, while there are a number of less common causes

(Table 9.2). In the elderly dialysis patient, blood loss, B_{12} or folate deficiency, and a primary bone marrow disorder such as myelodysplastic syndrome may be more apparent than in a younger individual.

Investigating a patient who is hyporesponsive to ESA therapy merits a stepwise approach (Fig. 9.2). If the patient is self-injecting, then adherence with the prescribed treatment should be questioned and confirmed. The reticulocyte count may give a clue as to whether there is a primary problem with erythropoiesis, or whether the bone marrow is already working effectively, thus suggesting a shortened red cell survival as a result of bleeding or hemolysis.

The possibility of either absolute or functional iron deficiency (see below) should be considered, and if there is any doubt, then a trial of increased intravenous iron may be helpful. A raised C-reactive protein may suggest active infection or malignancy, particularly in the elderly, and this should be vigorously investigated. Occult

Table 9.2 Causes of a poor response to ESA therapy

Common	Less common
Iron deficiency Inflammation (infection/malignancy) Blood loss	B_{12}/folate deficiency Hemolysis Marrow disorders, *e.g., myelodysplastic syndrome* Under-dialysis ACE inhibitors Hypothyroidism Anti-EPO antibodies (PRCA)

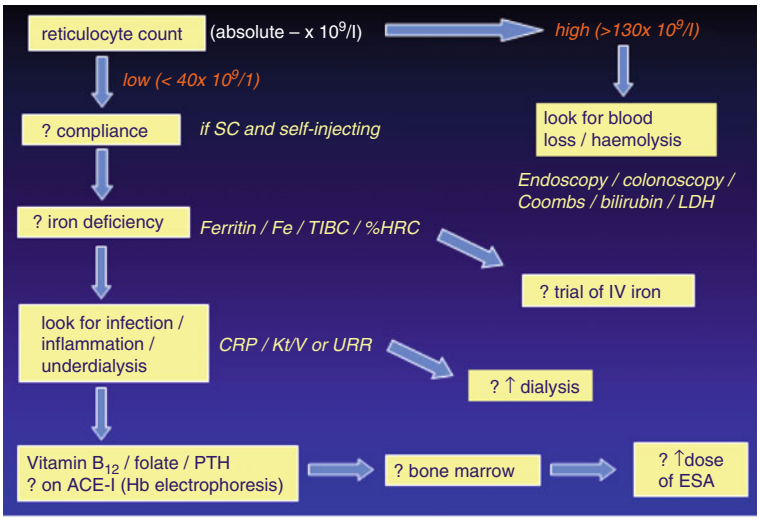

Fig. 9.2 Investigation of a poor response to ESAs

conditions such as tuberculosis or malignancy should also be considered, although these may prove somewhat elusive to detect. An increase in dialysis prescription and/or a change from conventional hemodialysis to hemodiafiltration may be of benefit. Screening for vitamin B_{12} or folate deficiency, blood loss, or hemolysis may be indicated, particularly in the elderly. A sharp fall in hemoglobin coupled with a very low reticulocyte count should alert the physician to the very rare condition of antibody-mediated pure red cell aplasia. Bone marrow examination may be required to exclude some hematological conditions such as myelodysplastic syndrome, very common in the elderly. A higher reticulocyte count makes it more likely that bleeding or hemolysis is the cause and a full hematinic screen and possible gastrointestinal investigations may be indicated (Fig. 9.2).

Whereas previously, physicians tended to escalate the dose of ESA therapy to higher and higher levels, recent randomized controlled trials have suggested possible harm in using high doses in ESA-resistant patients. It is still not clear whether the poor outcomes in this situation are due to the high doses of ESA therapy per se or whether this simply represents a group of patients who are generally more ill. Nevertheless, repeated dose escalation is no longer advised, and a maximum dose of epoetin of around 15,000 units per week in divided doses seems reasonable. This translates into a weekly dose of approximately 75 mcg of darbepoetin alfa or a monthly dose of approximately 300 mcg of pegylated epoetin beta.

Iron Management

Elderly patients are more prone to iron deficiency than their younger counterparts, and patients on dialysis are known to be in significant negative iron balance (Fig. 9.1). Thus, whereas healthy individuals lose 1–2 mg of iron per day via mucosal cell shedding in the gut, dialysis patients may lose up to four or five times this amount. Since dietary or orally administered iron is not absorbed due to hepcidin overactivity [7], intravenous iron has become mandatory in this patient population.

For the last two decades or so, iron deficiency has been categorized as being either *absolute* or *functional* (Table 9.3).

Absolute iron deficiency implies that there is a deficiency in total body iron stores, such that there are inadequate levels of iron to supply the bone marrow. The two types of iron deficiency are often compared to a bank account. Absolute iron

Table 9.3 Definition of absolute and functional iron deficiency

Absolute	Functional
Reduced body iron stores Low serum ferritin levels	Normal body iron stores but a failure to release iron rapidly enough to satisfy demands of bone marrow Normal/high serum ferritin ↓ Transferrin saturation (<20 %) ↑ Hypochromic red cells (>10 %)

deficiency implies that there is simply not enough money in the bank to be able to make a withdrawal.

Functional iron deficiency is a condition in which there are normal or even increased levels of total body iron stores, but there is a failure to mobilize this iron for use by the bone marrow for erythropoiesis. To continue the bank account analogy, functional iron deficiency is illustrated by a condition in which there is an ample amount of money in a savings account, but it cannot be withdrawn on demand.

Functional iron deficiency is much more common in the dialysis population, due to the chronic inflammatory state which upregulates hepcidin production by the liver (Fig. 9.3). Hepcidin is the master regulator of iron availability and its production is stimulated largely via interleukin-6 [7]. Hepcidin exerts its physiological effect by binding to the cellular iron export protein, ferroportin, thereby shutting down any iron efflux from cells responsible for iron transport, such as duodenal enterocytes, macrophages, Kupffer cells, and splenocytes [7]. The administration of intravenous iron circumvents the hepcidin-induced blockade of iron availability.

There are many laboratory tests available for the detection of iron deficiency, but none is ideal. The serum *ferritin* is a marker of body iron stores, and a very low serum ferritin level is diagnostic of absolute iron deficiency. Unfortunately, ferritin is also an acute phase protein and is elevated in chronic inflammatory states, as occurs almost ubiquitously in dialysis patients. Thus, a normal or even high ferritin level does not exclude the possibility of functional iron deficiency.

The *transferrin saturation* is also used as a marker of iron status, and levels of below 20 % are suggestive of iron insufficiency. However, levels of this parameter may fluctuate, and the absolute cutoff that will exclude functional iron deficiency or a response to additional intravenous iron is unclear.

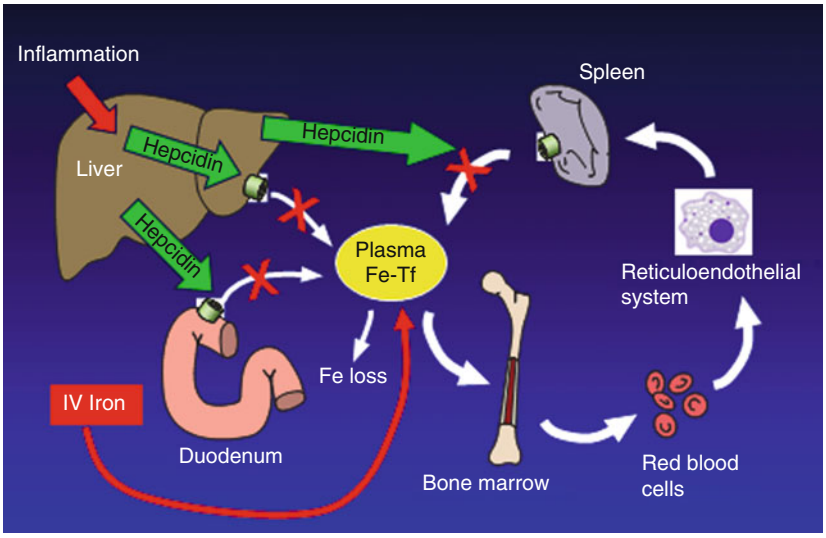

Fig. 9.3 Role of hepcidin in regulating iron supply in dialysis patients

The *percentage of hypochromic red cells* in the circulation has also been used as a marker of iron sufficiency but requires to be analyzed on a fresh sample. Thus, any delay in the sample reaching the laboratory may cause a serious elevation of this parameter. However, levels of <10 % should alert the physician to the possibility of iron insufficiency. Measurement of *reticulocyte hemoglobin content* uses a similar flow cytometric technique, with levels of <29 pg/cell suggestive of iron deficiency.

Since iron insufficiency is common in dialysis patients, supplementation of body iron stores is often required, and since this cannot be achieved by oral iron, intravenous iron replacement has become the standard of care in this population. Not only does this guarantee a readily available supply of iron, but it is extremely easy to administer to a hemodialysis patient who already has vascular access in situ. Thus, intravenous iron is usually administered during the dialysis session. There are many different intravenous iron preparations available worldwide. The older iron preparations such as iron dextran carry a small but definite risk of anaphylaxis due to preformed dextran antibodies; this has been found to be more prevalent with high-molecular-weight iron dextran compared to low-molecular-weight iron dextran compounds. Iron sucrose has been used for many years and has passed the test of time, being given to millions of patients worldwide. The usual administered dose is 100 or 200 mg, as tolerance at higher doses is reduced. Sodium ferric gluconate is also used in the dialysis population, mainly in the United States, Italy, and Germany. Several new intravenous iron preparations have recently been licensed, including ferric carboxymaltose, iron isomaltoside, and ferumoxytol. The main advantages of these preparations are that they can be administered in a higher dose over a shorter period of time, but their main applicability is in the nondialysis patient population. The amount of iron that dialysis patients require is not clear, but anemia guidelines suggest maintaining a serum ferritin level of somewhere between 200 and 500 ug/L, a minimum transferrin saturation of 20 %, and a minimum percentage of hypochromic red cells of 10 %. It is, however, clear that some patients respond to intravenous iron above these minimal thresholds, with an enhanced erythropoietic response. Whether or not this is harmful is not clear, and there are concerns that the liberal use of intravenous iron may exacerbate oxidative stress and infections. There is indeed evidence that intravenous iron administration may enhance bacterial proliferation and also reduce neutrophil function and for both of these reasons, IV iron should be withheld in patients with an acute bacterial or fungal infection.

Blood Transfusions

As outlined in the Introduction, blood transfusions were the mainstay of anemia management in dialysis patients prior to the introduction of recombinant human erythropoietin. Given the recent safety concerns with erythropoiesis-stimulating agents, however, there has been a recent increase in the use of transfusions in dialysis patients once again. In the elderly population, there is less concern about HLA sensitization than there is in the younger patient waiting for a kidney transplant, and

there are also many conditions more prevalent in the elderly which can only be managed by intermittent transfusions (such as myelodysplastic syndrome and advanced hematological or solid-organ malignancy).

Blood transfusions also have a role in conditions causing sudden onset of anemia, such as acute blood loss or hemolysis. In patients who are septic and then become resistant to treatment with ESAs, blood transfusions may become necessary if the hemoglobin concentration becomes critically low.

There has been much debate over the years as to the trigger hemoglobin for administering blood during intercurrent illnesses, and the threshold has gradually decreased. Part of the reason for this is the outcome of several randomized controlled trials, which have not suggested any advantages in transfusing patients whose hemoglobin falls below 10 g/dL. There may even be harm in doing so, and the threshold for transfusion for stable conditions has fallen to around 7 g/dL. Indeed, a randomized controlled trial of two trigger hemoglobin concentrations for blood transfusion in the critical care setting (7 g/dL vs 10 g/dL) showed absolutely no benefit in transfusing patients at the higher hemoglobin trigger [18]. Even in the cardiac setting, when patients may be suffering from acute coronary syndrome, the use of blood transfusion above a hemoglobin level of 8 g/dL has been critically questioned. Thus, in the absence of acute bleeding, there is little indication to transfuse a patient above 7 or 8 g/dL unless a surgical procedure is planned in which significant blood loss might be expected.

Thus, in the modern era of anemia management, the focus is on the balance between ESA therapy, iron administration, and blood transfusions. The relative use of these three strategies should be selected for the individual patient, and many factors might influence this.

Conclusions

Anemia management in the elderly dialysis patient is not dissimilar to that in the younger subject and remains a balance among the use of ESA therapy, intravenous iron supplementation, and blood transfusions. There are, however, some specific differences that are relevant to the elderly population.

Nutritional deficiencies (vitamin B_{12}, folic acid, and particularly iron) are more common in the older patient, as is hypothyroidism. All of these deficiencies are easily corrected by the use of supplemental products. In the nondialysis setting, chronic inflammation is more common in the elderly, but whether this adds anything to the preponderance of inflammation induced by chronic dialysis is unclear. Blood loss may be more common in the elderly, as a result of gastrointestinal inflammation or malignancy. Several hematologic conditions are also more common in the elderly, and the most noteworthy of these is myelodysplastic syndrome which may be unresponsive to ESA therapy.

It is, however, likely that most patients will be treated with ESA therapy with or without supplemental intravenous iron and blood transfusions will be reserved for

those resistant to these measures or when there is an intercurrent acute fall in the hemoglobin concentration.

The choice of hemoglobin target for the patient should also be individualized, in an attempt to maximize the benefits of anemia correction, while minimizing potential harmful effects. Thus, in patients with a previous stroke or malignancy, caution should be exercised in minimizing the use and dose of ESAs, given the concerns about possible exacerbation of these conditions with such agents.

Key Points

- Common causes of anemia in the elderly include erythropoietin deficiency, iron deficiency, B_{12} and/or folate deficiency, chronic inflammation, blood loss, gastrointestinal mucosal inflammation, malignancy, and myelodysplastic syndrome.
- A very low serum ferritin level (e.g., < 20 ug/L) conclusively proves a diagnosis of absolute iron deficiency – there is no other cause.
- The target hemoglobin concentration for elderly dialysis patients receiving ESA therapy should be individualized but should be somewhere around 10–12 g/dL.
- In patients showing a suboptimal response to ESA therapy, the reticulocyte count may provide helpful information. If low, then erythropoiesis is probably suppressed or deficient, whereas a high reticulocyte count might suggest bleeding or hemolysis.
- IV iron should not be given to patients with acute bacterial infection.

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