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Anemia after Kidney and Other Solid Organ Transplantation

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Abstract

Anemia has long been known to be a complication of end-stage renal disease, leading to cardiovascular morbidity and mortality. Restored renal function after successful kidney transplantation should be associated with the complete correction of anemia.

There are only few data available on the real prevalence of anemia after kidney transplantation. But, since many transplanted patients have some degree of renal impairment, it can be assumed that they may also experience anemia as a complication. Accordingly, some recent studies have reported anemia in about one-third of transplanted patients, regardless of the length of the follow-up. Kidney function has been identified as the main determinant, but different transplant-associated factors may contribute to the development of anemia after kidney transplantation.

More recently, anemia has emerged as a major problem also among recipients of non-renal solid organ transplantation. The event is mainly associated with the development of chronic kidney disease. Beside erythropoietin deficiency, immunotherapies as well as patient comorbidities contribute to anemia development. The incidence is 28, 50, and 65% among liver, heart, and lung transplant recipients, respectively.

Erythropoietin therapy is not contraindicated in solid organ transplantation, although clear information about the correct hemoglobin target is not available yet.

Correction of anemia is mandatory in order to reduce this threatening cardiovascular risk factor. **(Trends in Transplant. 2009;3:135-43)**

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Key words

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Kidney transplantation

Prevalence of posttransplant anemia

It is difficult to assess the exact prevalence of posttransplant anemia (PTA) as it is strictly dependent on the definition used.

In 1964 the World Health Organization (WHO)[1] set an official definition of anemia as a hemoglobin level less than 13 g/dl in men and less than 12 g/dl in women, regardless of age and menopausal status. For the KDOQI[2] and the United Kingdom Renal Association[3], men and postmenopausal women are anemic if their hemoglobin levels are less than 12 g/dl, while for a menstruating woman the lower limit is a hemoglobin level lower than 11 g/dl. Finally, for the Revised European Best practice Guidelines[4], anemia is defined if the hemoglobin level is two standard deviations less than the population mean.

With this wide variation of definition, it is no surprise that the reported incidences are so different. Furthermore, since many of the epidemiologic studies are cross-sectional or retrospective, the vintage of the transplant has to be taken into consideration.

One of the most important papers attempting to quantify the prevalence of PTA is a European cross-sectional survey involving 4,263 transplanted patients in 16 countries[5]. Anemia, defined according to the WHO criteria, was reported with a prevalence of 38.6%. Although 8.5% of patients were severely anemic, treatment was given only to 17.8%.

In other studies using different thresholds and times of measurement, anemia after transplantation ranged between 20 and nearly 40%, being very common especially among African American patients[6], and pediatric patients[7]. In this last group of patients, anemia has been observed at even higher rates: up to 60-83%.

Anemia develops earlier, more frequently, and more severely in patients with diabetic kidney disease[8].

Causes of posttransplant anemia

There are many potential causes of PTA[9].

A strong association has been demonstrated between hemoglobin level and poor graft function[10,11], but additional transplant-associated factors also contribute to anemia development. Among them: rejection episodes determining an increased inflammatory response, downregulated genes involved in erythropoiesis[12], bone marrow suppression either drug-related[13-15] or infection-related[16], female sex, folate and vitamin B_{12} deficiency, malignancy, erythropoietin (EPO) resistance, and absolute or functional iron deficiency due to uremia or chronic inflammation are very common[17]. Low ferritin (< 100 ng/ml) has been detected in 50% of transplanted anemic patients with chronic kidney disease stage 3-5, but not in stage 1[18]. It has to be said that in many cases anemia is multifactorial and there is a continuous overlap of different contributing factors.

After kidney transplantation, there is an immediate increase in EPO production[19]. This is not associated to an increased erythropoiesis, and precedes graft recovery. After this initial peak there is a smaller but long-lasting increase in EPO production, associated with an improvement in graft function and erythropoiesis. Erythropoietin production returns to normal levels after a hematocrit of 32% is reached[20]. Naive EPO production increases in anemic patients in comparison with non-anemic after transplantation[21].

Renal function

Almost every study considering the association between renal function and the presence of anemia after kidney transplantation have found one. The worse the graft function, the worse the anemia is.

It can be assumed that after the early posttransplant period, restoration of almost normal graft function should completely correct anemia. But, when the overall prevalence of anemia among kidney transplant recipients is compared to that observed in the general population with the same degree of renal impairment, the difference is almost 10-fold higher in kidney transplanted patients. Therefore, factors other than creatinine clearance contribute to the degree of anemia observed after transplantation[22].

Surprisingly, also in presence of normal kidney function, EPO deficiency and relative resistance can be causes of persistent anemia[23]. Even without a significant decline in renal excretory function, delayed graft function, acute rejection, or chronic rejection, it has been hypothesized that the possible long-term toxicity of calcineurin inhibitors may cause diminished EPO production[24,25], thus sustaining the incomplete anemia correction.

The application of the chronic kidney disease (CKD) classification to kidney transplant recipients has been recently adopted as a strategy to improve the long-term outcome of these patients. Several series have shown that the estimated glomerular filtration rate (GFR) of a well-functioning transplanted kidney falls into the grade 2-3 of the CKD classification[18,26-28] and this is inevitably associated to a number of comorbid conditions including anemia. Reduced renal function and metabolic acidosis[11] seems to play an important role in anemia of the long term. Very often the suboptimal correction of this complication, together with other comorbid conditions, causes a dramatically reduced patient survival after graft failure[29].

Impact of anemia on patient and graft survival

A recent paper tried to determine the impact of one-year PTA upon long-term patient and graft survival. In a cohort of 339 patients included in the study, 31.8% were anemic according to the WHO criteria. Independent predictors for one-year anemia were donor age and serum creatinine at six months. After a follow-up of 69.4 ± 17.4 months posttransplantation, a significant number of patients in the anemia group died (6.9 vs. 1.73%; $p = 0.04$) and a significant number of patients in the same group lost the graft (11.1 vs. 3%; $p = 0.004$). These results show that persisting anemia after transplantation is harmful in the long term for both patient and graft survival[30].

Lower hemoglobin levels were also associated with graft loss on multivariate analysis of data prospectively collected as part of the pharmacovigilance Long-Term Efficacy and Safety Surveillance project (LOTESS) of Novartis. This open, observational, cohort study included patients from 64 centers in the UK recruited between 1995 and 1998 and followed prospectively for up to seven years. The database is limited to patients treated with microemulsion cyclosporine. In this study, on univariate but not at adjusted analysis, lower hemoglobin and hemoglobin variability were associated with mortality and with mortality and graft loss, respectively. The authors suggest that full correction of anemia to improve mortality is not justified in renal transplant recipients and that further study is mandatory to assess the effect of hemoglobin correction on delaying graft failure[31].

The death rate has been demonstrated to increase in anemic patients in previous studies[32]. The PTA cohort of patients showed

inferior patient survival and a higher proportion of cardiovascular death (6.3 vs. 2.2%; p = 0.017) in comparison with the non-PTA cohort. Twelve-months PTA (HR: 3.0; 95% CI: 1.3-6.7; p = 0.009), together with 12-months creatinine, age at transplantation and hepatitis virus C positivity, were associated with mortality. Finally, in a prospective study of 938 transplanted patients followed at a single centre and recently published[20], the hypothesis was tested of the association between anemia and mortality and graft failure defined as return to dialysis. During a four-year follow-up, both mortality and graft failure rate were significantly higher in patients with hemoglobin levels below 11 g/dl. Mortality was 18 vs. 10% for anemic patients (p < 0.001) and graft failure was 17 vs. 6% (p < 0.001) in comparison to non-anemic patients. At multivariate Cox proportional analysis, the presence of anemia significantly predicted mortality (HR: 1.690; 95% CI: 1.115-2.560) and graft failure (HR: 2.465; 95% CI: 1.485-4.090) after adjustment for several co-variables such as age, gender, pretransplant time on dialysis, and comorbidities including diabetes. Furthermore, each 1 g/dl decrement in serum hemoglobin level increased the odds of graft failure by 1.9% during the follow-up.

Liver transplantation

The prevalence of anemia in cirrhotic patients is due to various reasons.

The first is the presence of expanded plasma volume and portal hypertension[33,34]. Patients with alcoholic cirrhosis have low folate levels when compared to nonalcoholic (35 vs. 9%). Other causes include the reduced red blood cell survival[35]; hemolysis due to enlarged spleen[33], renal insufficiency[36] and finally the ability to secrete erythropoietin in response to anemia is often defective in many patients with end-stage liver disease[37].

After orthotopic liver transplantation (OLT), anemia ranges between 4.3 and 28.2% depending on the definition used. In prospective trials evaluating different immunosuppressive regimens, the incidence of anemia ranged between 1 and 53%[38].

In a recent study by Guitard, et al.[35], the authors evaluated the prevalence/incidence and the risk factors for anemia at six months and one year after OLT in 97 consecutive transplants in 88 patients. Anemia, defined according to the WHO criteria, was present in 64.5, 50, and 47.8% of patients before and at month 6 and month 12, respectively, after OLT. But in the same study, considering the hemoglobin cut off for anemia below 11 g/dl, a total 41.8% of recipients were anemic before transplantation, with anemia decreasing to 13% at month 12 and being treated in only 33 and 30.3% of patients at month 6 and 12, respectively. The median weekly dosage of darbepoetin was 60 and 30 µg at the considered time intervals, with a corresponding epoetin dose of 5,000 and 20,000 U, respectively. Iron deficiency was uncommon, affecting only 14% of patients before transplant, and 10.5 and 8.3% at month 6 and 12, respectively, after OLT.

At multivariate analysis, mean corpuscular volume (< 85) at day 7, daily steroid dosage (< 0.3 mg/kg), serum creatinine (>130 µmol/l) and Hb level (< 11 g/dl) at month 1 were independent predictive factors for anemia at month 6. Daily steroid dosage (< 0.3 mg/kg), hematocrit (< 33%), red blood cell count at month 6 (< 3.75.000 mmc), daily dosage of cyclosporine at month 1 or tacrolimus and OLT for causes other than alcohol abuse, were predictive factors for anemia at month 12.

Also among OLT patients, renal function is the strongest independent predictive factor for anemia at month 6, with an odds ratio of 13.2 (2.0-86.9; 95% CI) for creatinine at month 1 above 130 µmol/l. Plasma creatinine loses its power at month 12, when renal function seems

not to have the same prognostic importance in comparison to other variables. This may be due to the fact that in this cohort of patients, a few are still experiencing some degree of renal impairment in the early posttransplant period, which is not present in longer follow-up.

The importance of the analysis carried out by Guitard is that this study excludes biases such as treatment with pegylated α interferon or ribavirin because none of their HCV-positive patients received these therapies within the first year after transplantation. In fact, it has to be considered that over 70% of HCV-positive patients receiving antiviral therapy develop anemia.

As for kidney transplantation, multiple etiologies or unrecognized causes may explain anemia also among OLT patients. But rare causes unique to transplantation include aplastic anemia, parvovirus B19 infection, graft-versus-host disease (GVHD), and posttransplant lymphoproliferative disease (PTLD).

Aplastic anemia

Aplastic anemia has been associated to hepatitis since 1955, with more than 200 cases reported in the following years. This kind of anemia has an incidence ranging between 5-33% in patients transplanted for hepatic failure secondary to "non-A, non-B, non-C hepatitis"[39]. In contrast, the incidence of aplastic anemia is 1-2/1,000 patients if the acute viral hepatitis does not lead to liver transplantation. The overall incidence of aplastic anemia is 7/100,000 patients in large studies including all the etiologies of liver failure requiring OLT[40].

Parvovirus B19 infection

Liver transplant recipients, as all other solid organ transplant patients, are susceptible to parvovirus B19 infection or reactivation either from donor or blood products[41]. In some studies, 32% of liver transplant recipients had evidence of parvovirus B19 viremia, but the association between infection and anemia was not clear[42]. Similarly, only 1.8% of pediatric patients showed an association between anemia and parvovirus B19 infection[43]. At present, evidences indicate that there is no clear association between parvovirus B19 infection and anemia after OLT, even though parvovirus B19 infection still has to be considered a potential cause of posttransplant anemia.

Graft-versus-host disease

Graft-versus-host disease (GVHD) is another uncommon cause of anemia, affecting approximately 1% of liver transplant recipients and carrying a poor prognosis[44]. Patients typically develop fever, skin rash, diarrhea, or pancytopenia within 2-6 weeks after transplantation. In this series, 11 out of 12 patients among 1,082 liver transplant recipients died. Risks factors for developing such a complication are age above 65, recipient with a donor more than 40 years younger and a closer donor/recipient HLA matching. Death is usually from infectious complications, bleeding or severe metabolic disorders resulting from severe diarrhea and reaches 75% of cases.

Posttransplant lymphoproliferative disease

Posttransplant lymphoproliferative disease (PTLD) is a complication arising typically after solid organ transplantation and often related to Epstein-Barr virus (EBV) infection. It includes a group of lymphoproliferative diseases ranging from benign polyclonal B-cell proliferation to malignant monoclonal lymphomatous lesions. The first presenting symptom is autoimmune hemolytic anemia. The overall incidence is different according to the type of graft. Overall incidence among OLT recipients

is 2-3%[45]. In large series, mortality is approximately 50%[46]. The mainstay of treatment is the immunosuppression drug reduction or discontinuation together with chemotherapy, and more recently, anti-CD20 monoclonal antibodies, radiotherapy and very seldom surgery. This high-risk population includes patients with previous antilymphocyte antibody treatment, EBV-seronegative patients, and pediatric patients. In children requiring antilymphocyte treatment, the risk of developing PTLD rises up to 30%.

Treatment options

Anemia treatment depends strictly on the determining cause. Nevertheless, a few considerations about recombinant EPO in liver transplantation may be useful.

Erythropoietin is reported to have a protective effect on ischemia and reperfusion models also in animal liver models; the administration of EPO a few minutes before ischemia leads to a reduction in liver injury[47].

Furthermore, since cyclosporine inhibits EPO production in experimental models, some authors investigated whether EPO production was impaired in liver transplant patients receiving treatment with calcineurin inhibitors: cyclosporine or tacrolimus. Using multiple linear regression models, the polynomial relationship between hematocrit and serum EPO values was similar to the control group in patients treated with tacrolimus, whereas EPO production was significantly reduced in patients receiving cyclosporine-based immunosuppression. Hematocrit and the type of calcineurin inhibitor were the only parameters independently related to EPO levels[48].

These results have important consequences, especially in the treatment of OLT patients needing antiviral therapy with ribavirin. In fact, a high percentage of these patients withdraw from treatment because of symptomatic anemia[49]. In conclusion, recombinant human erythropoietin (rHuEPO) can be effectively administered also among OLT recipients, but further clinical study will be necessary to evaluate the full therapeutic properties, the risk, if any, and the optimal target level of hemoglobin.

Heart transplantation

Reduced hemoglobin levels after heart transplantation is a common finding[50].

Potential causes of anemia in heart transplantation are common to other solid organ transplantation: iron or vitamin B_{12} deficiency, folate deficiency, perioperative blood loss, hemodilution, malnutrition, bone marrow suppression caused by inflammation, immunosuppressive drugs, and renal impairment. A peculiar clinical situation, though, distinguishes patients undergoing heart transplantation in comparison to other solid organ recipients. The interaction between chronic heart failure, renal failure, and anemia forms a vicious cycle named the cardio-renal anemia syndrome[51,52]. The interaction between these three conditions causes deterioration of the cardiac and renal function and increases anemia; each of the three can cause or be caused by the other so that virtually any patient with heart failure eligible for heart transplantation is anemic.

Anemia and low hemoglobin levels are both known to be risk factors for survival in several cardiovascular disorders such as myocardial infarction and heart failure[53,54].

Among heart transplant recipients, anemia is found to have a prevalence of about 70%[55] and up to 91.6% if standard definition is used[56]. A very similar prevalence of anemia has been reported also for pediatric recipients[57]. In heart transplant recipients, there is a significant inverse correlation between creatinine

and creatinine clearance and hemoglobin levels (p = 0.01) and also a strong trend for inverse correlation between creatinine and EPO levels[58]. Contrary to other cardiovascular disorders, low hemoglobin levels after heart transplantation do not represent an independent risk factor for reduced survival, but the demonstrated correlation is primarily caused by concomitant functional renal impairment[59]. Low hemoglobin levels were not associated with low leukocyte or thrombocyte count, indicating that there was not hemodilution as concomitant cause, nor did they represent a consequence of overall bone marrow suppression caused by antiproliferative medication.

Low EPO levels have also been detected in most heart transplant recipients[58]. When administered, EPO therapy resulted in increased hemoglobin levels and improvement of quality of life in 75% of patients, allowing effective anemia management.

Lung transplantation

There is a paucity of information regarding chronic anemia after lung transplantation, particularly as it relates to chronic renal insufficiency. However, the reported prevalence is about 65%[60] with 31% of heart and lung transplant recipients showing significant anemia with hemoglobin less than 10 g/dl in a single-centre experience[61]. Anemia is normochromic and in the majority of cases normocytic with normal reticulocyte count. Iron deficiency with a transferrin saturation below 20% was found in 35% of patients. Erythropoietin levels were significantly decreased in anemic lung transplant recipients, compared to non-transplanted iron-deficient patients. Non-anemic lung transplant recipients showed significantly lower EPO levels as compared with normal controls. No variables including plasma creatinine appeared to be a prognostic factor. Only female sex showed a trend toward higher EPO levels[60].

The demonstration of low EPO levels offers a rationale for treatment of chronic anemia with recombinant human erythropoietin (rHuEPO) also for lung transplant recipients. In a letter to the Editor published in 1994, End, et al. reported their first experience with rHuEPO therapy after lung transplantation[62]. They treated only four patients with a mean initial hematocrit level of 26%. Therapy was started 10-50 weeks after transplantation. Hematologic parameters increased significantly with mean hemoglobin after treatment, ranging between 12 and 13.5 g/dl. No side effect was experienced. Because of different individual responses, the duration of treatment was 1-15 weeks (median 5). In three patients, after anemia correction, treatment was stopped due to sustained stable hemoglobin levels above 10 g/dl. Mean single rHuEPO dose was 58 IU/kg.

The authors recommend rHuEPO treatment in lung transplanted patients with chronic anemia, either to prevent the potential risk of transfusion-transmitted viral infection, or to save blood products.

Conclusions

Anemia after kidney and solid organ transplantation is mainly but not only related to renal function. The best prevention should be the use of all the available measures aimed at protecting and maintaining a good renal function also among kidney transplant recipients. Several other equally important factors, some of which are unique to the transplant environment, can contribute to the appearance of this complication. Prompt identification and, where possible, successful correction, leads to anemia resolution.

Nevertheless, if PTA occurs it has to be treated immediately regardless of the type of transplanted organ, particularly in symptomatic patients or in patients with hemoglobin levels below 10 g/dl.

Still we are lacking large, well designed, prospective studies that can answer questions about response to treatment, hemoglobin target, risks if any, costs, and choice among the different erythropoiesis stimulating agents .

At present, even though many of the potential benefits of anemia correction have been demonstrated, the available literature still reports a surprisingly low rate of correction of this complication that affects half of the whole transplanted population and is a threat to patient and graft survival.

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