Anemia Management and Outcomes in Kidney Transplant Recipients

By Ahmed A. Awan, Wolfgang C. Winkelmayer, and Bhamidapati V. Murthy

Posttransplantation anemia (PTA) is an oft-neglected aspect of posttransplantation care that is associated with adverse outcomes for the kidney allograft and the recipient. The prevalence of anemia in kidney transplant recipients (KTRs) is very high, ranging from 25% to 40% depending on the definitions used, parameters measured, and average time since transplantation across study populations (1–3). The American Society of Transplantation (AST) and the World Health Organization have defined anemia as hemoglobin <13 g/dL in men or <12 g/dL in women. On the basis of these definitions, at the time of kidney transplantation, the majority of patients have anemia due to chronic kidney disease (CKD)–related erythropoietin (EPO) deficiency and resistance and also iron deficiency.

The customary treatment targets for the correction of anemia in CKD patients also do not apply to normalize hemoglobin concentrations. After successful kidney transplantation, endogenous production of EPO may increase, and resistance to EPO may decline with improvement in the uremic milieu, leading to resolution of anemia 3 to 6 months after transplantation. However, the majority of KTRs have allograft function that corresponds to CKD stages 3 through 5, and they have persistent anemia for as long as 6 to 12 months after transplantation (late PTA).

Consequences of PTA
Cardiovascular disease remains the leading cause of death among KTRs (4), and some studies have purported a relation between PTA and cardiovascular death (5). A relationship between PTA and mortality has been described in some studies (6, 7), whereas others have found no such association (8). Mohlar et al. (7) followed up 938 KTRs for 4 years and showed that all-cause mortality was 69% (95% confidence interval: 12% to 156%) higher in patients with anemia (per AST definition) at baseline. Conversely, a prospective study of 438 KTRs followed up for >7 years reported that a hemoglobin concentration <10 g/dL was not associated with increased mortality or graft loss (9). However, an association of PTA with increased risk of graft failure has been shown quite consistently (6–8). The adverse effects of anemia on quality of life are well known, and findings have been replicated in patients with PTA (10).

Causes of PTA
Besides the risk factors for anemia shared with CKD patients who have not undergone transplantation, PTA has a unique set of additional causes. Although every effort should be made to determine the precise cause of a patient’s PTA, it usually is a multifactorial process. Transplant function is the most important correlate of anemia, and anemia worsens as graft function declines (3, 11). Transplant recipients who experience rejection episodes or have more than one transplant have a higher incidence of anemia (12). In the immediate posttransplantation period, surgical blood loss and induction immunosuppression contribute to anemia, and delayed graft function can amplify the problem.

Late PTA can be due to several causes (Figure 1). Anti- metabolites (azathioprine and mycophenolic acid) and mTOR inhibitors (sirolimus and everolimus) cause anemia by bone marrow suppression, and anemia is more severe when these two drug classes are combined. Interestingly, anemia of mTOR inhibitors presents with microcytosis. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, which are used in the treatment of posttransplantation erythrocytosis, also lead to PTA. Calcineurin inhibitors (tacrolimus and cyclosporine) can cause thrombotic microangiopathy. Donor-derived antibodies against recipients’ red blood cells can cause immune-mediated hemolysis (passenger lymphocyte syndrome), which is a rare cause of PTA.

Management and hemoglobin targets
When we consider the adverse associations of anemia with quality of life, graft survival, and possibly mortality, it would stand to reason that correction of anemia and normalization of hemoglobin could potentially mitigate these consequences. Intuitively, the initial step in management would be to identify any reversible causes, including iron deficiency, and treat them appropriately. However, some of the potentially causative factors of PTA are difficult to avoid, including the medications used for immunosuppression and infection prophylaxis.

One target amenable to therapeutic intervention is absolute or relative deficiency of endogenous erythropoietin, which can partly be treated by the administration of erythropoiesis stimulating agents (ESAs). Recent studies in animal models have shown that ESAs may prevent allograft nephropathy by mechanisms other than anemia correction, including preservation of intragraft expression of angiogenic factors, upregulation of antiprotective factors, and immunomodulating effects (13–15). Owing to a lack of randomized controlled trials of the effects of anemia correction in KTRs, the transplantation community has been relying mostly on data from patients with CKD and anemia. The enthusiasm about the use of ESA for anemia correction was curbed by findings from the Normal Hematocrit Study in patients receiving dialysis and the CHOIR, CREATE, and TREAT studies in non–dialysis-dependent CKD (16–19). These trials showed either no benefit or even cardiovascular harm with the use of ESAs to achieve higher hemoglobin concentrations. Consequently, the current guidelines for the management of PTA recommend following the targets suggested for anemia in CKD patients without a transplant while acknowledging the dearth of data in KTRs (20, 21).

An observational study by Heine et al. (22) retrospectively analyzed 1794 transplant recipients in the Austrian Dialysis and Transplant Registry and showed an increase in mortality if hemoglobin was corrected to more than 12.5 g/dL by the use of ESAs, thus reinforcing the trial data in CKD patients. Interestingly, patients with higher hemoglobin levels without the use of EPO had better survival rates in this study. However, this paradigm was challenged by two recent prospective studies showing a benefit of ESA use in KTRs. Choukroun et al. (23), in a randomized controlled trial, showed that targeting a hemoglobin level of 13.0 to 15.0 g/dL by using epoietin-β led to improved graft survival and quality of life without increasing the risk of adverse cardiovascular events.

In a recent randomized controlled trial from Japan, a hemoglobin target of 12.5 to 13.5 g/dL (with use of ESA) was associated with a reduction of decline in kidney function over a follow-up time of >3 years in the chronic phase of allograft nephropathy, without any serious adverse events (24). Of note, the target hemoglobin in the high-hemoglobin group was achieved after 18 months in this 3-year study. These studies are compared in Table 1. The contradictory results among various studies of ESAs in CKD and KTRs can theoretically be explained by the differences in baseline cardiovascular risk status, the doses of ESAs used, and the rate of correction of anemia, along with the immunologic and nonimmunologic mechanisms of anemia in KTRs that are different from those in patients with CKD without KTR.

In summary, the burden of PTA in KTR remains high and causes significant morbidity and mortality in these patients. Any PTA should be proactively addressed as part of holistic management of KTRs. Identifying a specific cause remains vital so that any reversible factors can be eliminated. The target hemoglobin and use of ESAs remain controversial, but recent evidence challenges the

Figure 1. Common causes of posttransplantation anemia

Drugs:
- ATG
- MMF/Azathioprine
- Sirolimus
- Ganciclovir
- ACEI/ARBs
- TMP/SMX

Immune Mediated Hemolysis:
- Passenger lymphocyte syndrome
- Immunosuppression
- Graft
- HLA
- Malignancy

Non-immune Hemolysis:
- G6PD Deficiency
- Exposure to drugs

Decreased RBC production

Immune mediated hemolysis

Non-immune hemolysis

Graft

Decreased RBC destruction

EPO deficiency/Resistance:
- Allergic reaction
- Iron/Potent/122 deficiency
- Anemia
- HIV
- TB
- Aplastic Anemia

MAHA:
- Tacrolimus
- Cyclosporine
- Sirolimus

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Table 1. Comparison of 3 recent studies analyzing ESAs in posttransplantation anemia

<table>
<thead>
<tr>
<th>Study description</th>
<th>Heine, et al., 2009 (22)</th>
<th>Choukroun, et al., 2012 (23)</th>
<th>Tsujita, et al., 2018 (24)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study design</strong></td>
<td>retrospective cohort study (Austrian Institute of Kidney Health) registry</td>
<td>open-label, multicenter, randomized controlled trial</td>
<td>open-label, multicenter, randomized controlled trial</td>
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<tr>
<td><strong>Setting</strong></td>
<td>Transplantation centers in Austria</td>
<td>17 centers in France</td>
<td>2 hospitals in Japan</td>
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<tr>
<td><strong>Participants</strong></td>
<td>1794 patients who received transplants between 1992 and 2004</td>
<td>120 patients who received transplants at least 12 months before enrollment</td>
<td>127 patients who received transplants at least 12 months before enrollment period of January 2012 to March 2014</td>
</tr>
<tr>
<td><strong>Number of kidney transplants</strong></td>
<td>Primary kidney allograft</td>
<td>Primary or secondary kidney allograft</td>
<td>Primary allograft (except one patient)</td>
</tr>
<tr>
<td><strong>Patients with cardiovascular disease at baseline</strong></td>
<td>Included</td>
<td>Included</td>
<td>Excluded</td>
</tr>
<tr>
<td><strong>Intervention group</strong></td>
<td>Erythropoietin</td>
<td>Epoetin-α to normalize hemoglobin (13.0–15.0 g/dL)</td>
<td>Darbepoetin-α or epoetin-β pegol to target hemoglobin 12.5–15.5 g/dL</td>
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<tr>
<td><strong>Control</strong></td>
<td>No erythropoietin</td>
<td>Epoetin-α to partially correct hemoglobin (10.5–11.5 g/dL)</td>
<td>Target hemoglobin 10.5–11.5 g/dL</td>
</tr>
<tr>
<td><strong>Type and dose of erythropoietin</strong></td>
<td>Not specified</td>
<td>Epoetin-β</td>
<td>Darbepoetin-α or epoetin-β pegol</td>
</tr>
<tr>
<td><strong>Hemoglobin target</strong></td>
<td>12.5 g/dL (cutoff)</td>
<td>13–15 g/dL vs 10.5–11.5 g/dL</td>
<td>12.5–13.5 g/dL vs 10.5–11.5 g/dL</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>Median 5.6 years (interquartile range 3.0–8.7 years)</td>
<td>2 years</td>
<td>3 years</td>
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<tr>
<td><strong>Mortality in intervention group</strong></td>
<td>Increased at hemoglobin &gt;14 g/dL</td>
<td>1 patient died (compared with 3 patients in control group)</td>
<td>None in either group</td>
</tr>
<tr>
<td><strong>Number of cardiovascular events in intervention group</strong></td>
<td>Increased</td>
<td>Low but similar to control group</td>
<td>None in either group</td>
</tr>
<tr>
<td><strong>Rate of mean decline in eGFR in intervention group</strong></td>
<td>Not evaluated</td>
<td>–1 mL/min/1.73 m² vs –5.1 mL/min/1.73 m² in low-hemoglobin group</td>
<td>–2.4 mL/min/1.73 m² vs –5.9 mL/min/1.73 m² in low-hemoglobin group</td>
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