Challenges in the Management of Failing Kidney Graft

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Patients with a failed kidney allograft have steadily increase in recent years and returning to dialysis after graft loss is one of the most difficult transitions for chronic kidney disease patients and their assistant physicians. The management of these patients is complex and encompasses the treatment of chronic kidney disease complications, dialysis restart and access planning, immunosuppression withdrawal, graft nephrectomy, and evaluation for a potential retransplant.

chronic kidney disease graft intolerance syndrome immunosuppression kidney graft failure

1. Introduction

The last decade has seen a marked improve in short-term kidney transplantation outcomes, but long-term graft survival remains sub-optimal over the last 30 years [1]. This has led to an increased prevalence of kidney transplant (KT) recipients with graft loss, currently the fourth leading cause of incident dialysis, that will likely increase over time [2][3].

Returning to dialysis after graft loss is one of the most difficult transitions for chronic kidney disease (CKD) patients and their assistant nephrologists, as the conditions of these patients are complex and they face several complications. Patients with allograft loss have lower quality of life scores, a higher burden of depression, increased hospitalization, and significantly higher mortality rates [4][5]. From a health care provider point of view, the transition of care from transplant to dialysis is haphazard and not-standardized. The decision on the right timing to start dialysis, vascular access management, the optimal immunosuppression (IS) withdrawal, the impact of graft nephrectomy and relisting for a subsequent transplant are fundamental issues to address.

Despite the large number of patients affected by the deleterious consequences of graft loss, the only available recommendations on the care of the patient with a failing graft are the 2014 guidelines from the British Transplantation Society [6].

The management of the failing graft has become a growing concern in the kidney transplantation community and several groups are arising to address this complex issue. The development of multidisciplinary teams and a paradigm shift focusing on long term patient outcomes, combined with advances in immunosuppressive drugs and modern immunogenetic techniques are contributing to provide the best care to patients with graft loss.

2. Management of the Failing Allograft

2.1. Definition of a Failing Allograft

The definition of a failing allograft is the beginning of the challenge in managing KT recipients with decreased glomerular filtration rate (GFR). The Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines suggest that KT recipients with CKD stage 4T, in evidence of progression, should be prepared for kidney replacement therapy [7]. However, estimated GFR (eGFR) formulas have been derived from non-transplant patients and seem to be inaccurate in KT patients [8]. The GFR decline in patients with allograft dysfunction is also less predictable then transplant-naïve incident dialysis patients [9][10]. A recent study analyzed the variability of eGFR, assessed by most of the available equations, in reflecting measured GFR changes in KT patients, defined by repeated determinations of iohexol clearance. They found that eGFR, both by creatinine and/or cystatin-c formulas, was unreliable in reflecting real GFR changes over time [11].

A combined approach that includes eGFR trends, proteinuria, the presence of donor-specific antibodies (DSA), recurrent disease and transplant glomerulopathy might be the best predictor of graft failure [12][13]. A multicenter group have evaluated the four-variable (age, sex, eGFR and urine albumin-to-creatinine ratio) kidney failure risk equation in KT recipients, and concluded that the equation accurately predicts graft failure, especially in patients with eGFR < 45 mL/min/1.73 m^2 [14].

Another issue is the heterogeneity of causes of allograft failure and difficulty in defining the cause of graft loss. A recent study that thoroughly analyzed the cause of death-censored graft failure in 303 recipients, concluded that 51.2% of the patients had more than one cause contributing to graft loss and that the causes varied over time [15]. Focusing solely on the Banff criteria is difficult since most patients with progressive graft loss are not routinely submitted to late biopsies, and when biopsies are available, cumulative histological injuries coincide and accumulate. [16] Additionally, there are important contributors to graft failure such as aging or cardiovascular disturbances that are underrated in a histology focused practice [15][17].

2.2. Chronic Kidney Disease Management

There are important dichotomies in CKD management between transplant-naïve patients and transplanted patients. The main focus of transplant nephrologists is to prolong allograft survival, which comes at the expense of a worst control of CKD-associated complications and a less organized beginning of dialysis. Higher blood pressure, anemia, CKD—mineral bone disorder (CKD-MBD) and worst nutrition contribute not only to higher morbimortality, but also play an important role in allograft dysfunction progression [18].

Focusing on anemia, the benefit of using erythropoiesis-stimulating agents (ESA) and the optimum target hemoglobin remain uncertain in transplant patients [7]. A randomized clinical trial (RCT) evaluated the use of ESA in KT recipients with a mean eGFR of 35 mL/min/1.73 m^2. The ESA group showed significantly higher levels of hemoglobin (12.5–13.5 g/dL vs. 10.5–11.5 g/dL) and a significantly slower rate of eGFR decline, without significant side effects [19].

The diagnosis and management of CKD-MBD in KT is very complex as it encompasses bone disease before KT, bone disease after KT, and the influence of immunosuppressant drugs, especially steroids [20]. KT recipients have a five-times-higher risk of bone fracture than general population, which represents an important contributor to morbidity and mortality [21]. There is no consensus on the most prevalent type of bone disease, and bone biopsy studies on KT recipients have small sample sizes and conflicting results [22][23][24]. The KDIGO guidelines recommend the evaluation of phosphorus and calcium every 1–3 months, and parathormone every 3–6 months in CKD-5 KT recipients and for patients with a higher risk of osteoporosis and bone mineral density assessment if results alter therapy. The recommended treatment for CKD-MBD is similar to patients without KT, but the level of evidence is “not graded” [25].

Volume overload and dyslipidemia may also be important contributors to the progression of graft dysfunction and cardiovascular mortality. Data from the UK renal registry showed that the majority of KT recipients with eGFR < 30 mL/min/1.73 m^2 did not reach target levels regarding blood pressure or LDL levels [26].

A definitive dialysis access, especially for hemodialysis (HD), is another important issue in KT recipients returning to dialysis. Several scholars have reported that KT recipients start HD by a CVC more frequently than arteriovenous fistula, and a large registry study concluded that 65% of patients restart dialysis using a CVC [27][28]. Considering that KT patients are immunosuppressed and have a higher incidence of infection, these findings are alarming and need to be addressed [29]. A recent large cohort study concluded that resuming dialysis with a CVC is an independent risk factor for mortality after graft loss [4]. The worst management of CKD-related disease continues more than 1 year after dialysis resuming, and patients with a previous KT have the worst dialysis quality metrics compared to transplant-naïve patients, having a major impact on morbidity and mortality [4][30][31].

2.3. Individualized Care to a Patient with a Failing Allograft and Strategies to Defer Dialysis

The British Transplantation Society recommends the development of dedicated low clearance transplant Clinics, which provide multidisciplinary tailored care from both a transplant and a low clearance perspective, including specialized nephrologists, nurses, dietitians and pharmacists [6]. Two studies accessed the benefits of low clearance transplant clinics in graft failure recipients’ outcomes. No differences were found regarding clinical or biochemical parameters, retransplantation or mortality, but patients followed in low clearance clinics received more counselling regarding dialysis modality, less unplanned dialysis starts and more prompt transplantation work-up [32][33].

This individualized multidisciplinary approach is more focused on long-term outcomes and brought some novelties with regard to differing eGFR decline, prolonging residual renal function and improving patients’ quality of life [34].

Focusing on stabilizing eGFR, calcineurin inhibitor (CNI)-free regimens could be beneficial considering their nephrotoxicity and metabolic side effects, despite a higher risk of acute rejection and HLA sensitization [35][36][37][38]. The BENEFIT and BENEFIT-EXT trials have shown that de novo belatacept-based immunosuppression is

associated with better renal function and less chronic allograft nephropathy compared with cyclosporin schemes [39][40]. The benefits of belatacept conversion in patients with longer post-transplant time to attenuate previous CNI toxicity is not well-established. A retrospective study analyzed the role of belatacept as a rescue therapy in patients with chronic graft dysfunction (mean eGFR = 22 ± 9.4 mL/min/1.73m^2) and found a significant increase in eGFR (32 ± 13 mL/min/1.73m^2), improvement in serum bicarbonate levels, better CKD-MBD control, and an increase in albumin levels [41].

Incremental HD strategy is another novelty with the goal of preserving residual renal function on patients with a failing graft. Although there are no published RCT studies available, recent recommendations believe that it might be beneficial by extrapolation of native kidney CKD patients [34][42].

2.4. Dialysis Timing, Modality and Conservative Care

Studies on the optimal timing of dialysis initiation after graft failure are lacking. A cohort study that evaluated 4741 patients with graft failure showed that higher eGFR at dialysis restart was associated with higher mortality [43]. However, there was an important confounder since the most ill patients with more comorbidities started dialysis sooner.

The majority of patients with graft loss who resume dialysis opt for HD, but when compared to native kidney patients, there are more KT recipients choosing peritoneal dialysis (PD), probably due to age and autonomy bias [44][45]. A large, matched cohort study, performed by the French Language Peritoneal Dialysis Registry, compared 328 PD incident patients who experienced graft loss with 656 matched transplant-naïve patients and concluded that, despite similar peritonitis rates, transplant patients had a significantly higher rate of PD technique failure. The main reason for HD transfer was adequacy and/or ultrafiltration failure [46].

Kidney palliative care is an emerging subspecialty of palliative care and nephrology, but for KT recipients, the utility of kidney palliative care has not been explored nor well-delineated. A recent small trial published by a group of inpatient kidney palliative care service (KidneyPal) showed that providing a trained and multidisciplinary team of palliative care to patients with graft failure increased the adherence of patients to palliative care and time-limited trial dialysis, resulting in a more active role of the patient to decide their future after graft loss [47].

2.5. Immunosuppression Withdrawal

Decisions on tapering immunosuppressive medications in patients returning to dialysis are complex, without a strong evidence base or universally accepted recommendation, resulting in widely clinical practice variance. The Kidney Recipient with Allograft Failure Transition of Care (KRAFT) group distributed an online questionnaire to 92 KT centers to evaluate the patterns of management of patients with renal allograft, concluding that practices in the US vary greatly [48]. Several studies have addressed the impact of IS withdrawal after KT failure, but the majority are small and retrospective or registry analyses with limited information on IS withdrawal. The first large observation study analyzed 119 consecutive patients with allograft failure and PRA < 20%, concluding that weaning IS was a triggering event to graft intolerance syndrome (GIS) and an independent predictor of HLA

sensitization independent of nephrectomy [49]. Other small retrospective studies have conflicting results, either in favor of [50][51] or opposed to IS maintenance [52][53].

A major difficulty in maintaining IS after graft loss is the adequate dosing of CNI. In a study by Augustine and colleagues, the majority of the patients who continued IS had a functioning pancreas graft and maintained higher levels of CNI, which might explain the lower HLA sensitization [49]. Additionally, a recent trial that included 45 patients with graft loss that maintained tacrolimus for 24 months, showed that higher tacrolimus levels (≥3 mg/dL) were protective against allosensitization [51].

2.6. Graft Nephrectomy

When an established indication of graft nephrectomy is not present, the reported rate of surgical allograft nephrectomy after graft failure varies from 9 to 74%, depending on the center policy rather than compelling data [54] [55]. The potential benefits of allograft nephrectomy include the prevention of GIS, the possibility of IS withdrawal, and making more room for a new graft. The risks are loss of residual renal function, HLA sensitization, and surgical morbidity and mortality [56]. There are two opposing theories concerning HLA sensitization and graft nephrectomy: the failing graft can trigger HLA antibodies formation due to the continued exposure of non-self-antigens versus the “sponge theory” that the graft absorbs anti-HLA antibodies and decreases their serum detection [55][57]. In most cohorts, peak PRA levels are higher in patients who undergo allograft nephrectomy, including studies using single-antigen assays [53][55][58][59]. However, in many cases, graft nephrectomy occurs in the context of GIS after IS withdrawal, which might be a major sensitizing event [49].

2.7. Relisting for a Subsequent Kidney Transplant

In selected patients with appropriate clinical conditions to receive a new graft, retransplantation offers the largest survival benefit, with a mortality rate reduction ranging from 20% to 88%, depending on specific comorbidities and transplant era [60][61][62]. The British Transplant Society Guidelines recommend that patients suitable for retransplant should be evaluated when graft failure is anticipated within the next year, and ideally provide a preemptive retransplantation [6]. However, the access to a subsequent KT is frequently compromised by HLA sensitization, and a large number of young CKD patients with a previous KT are constantly waiting for a subsequent graft [63]. The access to retransplantation is a very complex and intricate topic that involves not only the assistant nephrologist and transplant surgeon, but also the immunologist and regional allocation laws.

3. Conclusions

With the increasing number of KT recipients returning to dialysis, the nephrology community is shifting towards a better paradigm and most transplant centers are now driven to deliver long-term, individualized care. The patient with a failing graft encompasses several issues that are similar to native kidney CKD patients, but longer dialysis vintage and exposure to IS make this population management more complex. New data on IS withdrawal

management, impressive progresses in immunogenetics and new pharmacological therapies are arising and bringing a new hope to CKD-5 patients with a failing graft.

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