

Palliative care in kidney transplant recipients with graft failure

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Abstract: Kidney transplantation is the best renal replacement therapy for patients with end stage kidney disease. It provides longer patient survival and better quality of life than dialysis. The clinical course after kidney transplantation could be complex and variable. Patients may develop various complications or even kidney graft failure. Symptom burden related to uraemia in patients with graft failure, and the side-effects of immunosuppression, cause psychological distress and adversely affect the quality of life of patients. Treatment decisions in patients with graft failure can be challenging to patients and their caregivers. Renal palliative care is an emerging field, but its adoption remains relatively low among kidney transplant recipients with progressive graft failure. In this context, timely consideration and referral for palliative care can improve symptom burden, reduce stress in patients and their caregivers, and facilitate treatment goal setting and advanced care planning. Common barriers to bring palliative care to suitable patients include: (I) misconception in patients, caregivers and healthcare providers that palliative care means abandonment of life sustaining treatment; (II) over-optimistic prognostic assessment and over-aggressive management approach; (III) insufficient awareness and training in palliative care of healthcare professionals; (IV) inadequate access to and insufficient resources in palliative care. Enhanced training and awareness, and further studies, would be needed to optimize the decision process and delineate the benefit of palliative care, and to guide evidencebased practice in the transplant population.

Keywords: Kidney; transplantation; palliative care; advance care planning (ACP); end-of-life-care

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Introduction

Background

Palliative care refers to the patient-centred approach to manage the physical, psychological, social and spiritual needs of patients and their families (1,2). The treatment goal of palliative care is not merely focusing on diseasespecific therapy but also achieving symptom control/relief, restoring functional capacity with the ultimate aim to maintain better quality of life of the patients with serious illness. Palliative care includes but is not limited to endof-life care. The process needs engagement of the patients and their caregivers in shared decision making from the outset.

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Rationale and knowledge gap

There was continuous improvement in long term outcomes of kidney transplant recipients (3). Despite the advances in transplantation, significant proportion of kidney transplant recipients remain in persistent limitations related to coexisting co-morbidities or transplant related complications (4). They also experience a range of adverse symptoms related to the use of immunosuppressant. The worry of graft failure and need to return to dialysis also adds the psychological burden to the kidney transplant recipients. In the past decades, the number of elderly prevalent kidney transplant recipients continues to grow worldwide (5). Frailty and multiple co-morbidities are not uncommon in the elderly population (6-8). Hence, holistic post-transplant care for these patients becomes one of the greatest challenges in the current era. Such care would not only involve disease specific management, but also management of various physical symptoms, psychological distresses and decision support according to the everchanging medical and psychosocial situations.

Objective

This review discusses the role of palliative medicine in kidney transplant care, delineates various important components of palliative care, and highlights the challenges in implementing palliative care to kidney transplant recipients.

Palliative care of patients with failing kidney graft

Challenges in management of patients with failing kidney graft

Definition of graft failure

Graft failure is commonly defined as failure of kidney graft function for any reason that ultimately requiring dialysis and/or re-transplantation. Despite continuous improvement of long term graft survival in kidney transplant recipients (3), substantial proportion of transplant recipients developed graft failure. In 2021, 11.3% of incident transplant waitlist patients in the United States had previous transplant (9). According to the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines, preparation for kidney replacement therapy shall be initiated in kidney transplant recipients with chronic kidney disease (CKD) stage 4T (10). However, most estimated glomerular

filtration rate (eGFR) equations are derived from nontransplant patients and lack accuracy in kidney transplant recipients (11,12). Furthermore, other transplant-specific factors such as presence of donor specific antibody, recurrent disease and transplant glomerulopathy also influence on the rate of graft function deterioration in kidney transplant recipients. The recent KDIGO Controversies Conference on Challenges in Management of Kidney Allograft from Decline to Failure recommended that dialysis shall be initiated based on clinical factors and symptoms rather than eGFR alone. They suggested eGFR of <20 mL/min per 1.73 m^2 is an appropriate time to initiate discussion on kidney replacement therapy/ conservative management (13). A multi-center cohort study identified eight different patterns of eGFR trajectories after transplantation (14). Trajectory-based assessment of kidney transplant patients may be useful for prognostication and determine optimal timing for graft failure management planning.

Increasing prevalent elderly kidney transplant recipients

The number of elderly kidney transplantation recipients continues to grow. In the United States, transplantation of adults aged above 65 years has more than 3-fold increase in past decades (8). These elderly recipients had inferior patient and graft survival when compared with younger counterparts (15,16). They were more likely to have multiple co-morbidities, and were prone to frailty and polypharmacy (7,17). Some elderly transplant recipients experienced accelerated decline in functional and cognitive status after kidney transplant (4). They were susceptible to complications and medication-related side effects (18). Survival benefit conferred by dialysis also diminished in these older, frail patients (19,20). On the other hand, they are more prone to dialysis related complications after dialysis initiation (21). Elderly and frail transplant recipients would probably face high morbidity and mortality after graft failure, regardless of choosing conservative management or dialysis (22). These factors pose significant challenges to the elderly recipients on decision making when they suffer from graft failure or approach end-of-life stage. Supporting these elderly patients and their families to formulate the treatment goal and care plan after graft failure would be needed.

Transition care for patients with declining allograft function

Discussion about future care plan (dialysis, re-transplantation



Figure 1 Integrating palliative care in the management of kidney transplant care. EOL, end-of-life care.

or conservative management) is an important but challenging process for patients who have declining allograft function. These patients often have past experience of dialysis before transplant, but they are going to face this situation again when they are older and medically more complex. It is known that patients with graft failure tend to have higher mortality risk after resuming dialysis when compared to the transplant naïve patients (21). Yet, Patients usually have own perceptions of dialysis based on past experience, and tend to overestimate benefit and underestimate harm of intervention (23,24). Hence, patients and their family should be primed about the potential future course with declining graft function. The decision of treatment plan shall be driven by patient's goal and preferences. Special care on immunosuppressant management, as well as their psychosocial aspect would be needed. An inter-professional and multidisciplinary team approach should be adopted to support patients who opt for conservative management (13,25).

Palliative care in kidney transplant recipients

Palliative care is an emerging field in nephrology. Yet, palliative care had been under-delivered to kidney transplant recipients (1,26,27). Previous studies demonstrated that these patients received intensive care more frequently and were less likely withdrawn from dialysis when developing graft failure. For patients who suffered from post-transplant malignancy or other terminal illnesses, they were also less likely engaged in discussion of end-of-life care planning and tended to continue on more aggressive life-prolongation

treatment (28). This could be due to the uncertain disease course and misunderstandings about palliative care among health care providers, patients and caregivers.

In the past, palliative care was synonymous with terminal care and positioned as a distinct entity that was separated from disease-specific care. In the 'traditional' model, initiation of palliative care requires the abandonment of life sustaining therapies before being eligible for palliative care. There is emerging evidence to demonstrate the benefits of early palliative care intervention in both malignant and nonmalignant conditions (29-32). Thus, palliative care can be offered simultaneously with, and complement life-sustaining care. It also provides symptom relief and minimizes distresses to patients and their caregivers. Current evidence suggests palliative care will not lead to adverse outcome to patients (33-36). It also facilitates setting goals of care, advance care plan and provides quality end of life care, particularly for patients who have terminal illnesses (such as malignancy) or kidney graft failure.

An integrated model of palliative care has been proposed for the transplant population (*Figure 1*). While on the standard post-transplant care to maintain stable graft function and manage post-transplant complications, kidney transplant recipients could also receive palliative care simultaneously that focuses more on symptom management, psychosocial support and quality of life improvement (1). When their conditions deteriorate, they would be supported for complex medical decision making or even proceed to end-of-life care. Primary palliative care can be delivered by renal physicians, but high need and complex cases would require input from palliative care team (37). All disciplines work together to provide holistic care that addresses the personal needs, including the spiritual and psychological health of the patients and their caregivers.

Symptoms assessment and management

Kidney transplant recipients experience high prevalence of adverse symptoms. Allograft dysfunction, side effects of immunosuppressant and post-transplant malignancy are the major contributors to their symptom burden (38). Despite the high prevalence of adverse symptoms experienced by kidney transplant recipients, these symptoms are often under-recognized and under-treated (37). Recognition of adverse symptoms is important as it would negatively impact on treatment satisfaction and clinical outcomes (39,40).

Side effect of immunosuppressant is a major source of adverse symptoms in kidney transplant recipients. Management of immunosuppressant, such as reduction or withdrawal, in patients with allograft function decline is an important strategy for symptoms control. This has to be personalized, taking into consideration of potential risks (such as infection and co-existing comorbidities), benefits (such as avoiding sensitization) and patients' preference. For patients who opt for conservative management, the treatment goal would be maximizing duration of functioning graft. Strategies such as calcineurin inhibitor minimization would be considered (12,13).

The emerging concepts of symptom management suggest a patient-centred approach. The first step would be accurate and reproducible symptom appraisal, which helps assess how unpleasant symptoms are perceived by different patients (41). There are validated tools for symptom appraisal. For instance, the NIH Patient Reported Outcomes Measurement Information System (PROMIS-57), a standardized patient-reported outcomes assessment tool that comprises 57 questions across seven health-related quality-of-life domains (physical function, anxiety, depression, fatigue, pain, sleep disturbance and social functioning), has been validated its application in kidney transplant recipients (42). These assessment tools facilitate effective symptom management with integrated symptom palliation strategies, instead of just focusing on the aetiological and mechanistic disease pathways (43,44).

Advance care planning (ACP)

For patients with graft failure, dialysis treatment can prolong life, but it also has physical, psychosocial and how they spend their time in end-of-life situation. ACP clarifies patient preference and facilitates treatment goal setting, at a time before urgent decision making is needed (18). ACP is a continuous iterative "process" rather than a one-off event. The process involves shared decision making with full respect of patients' autonomy. Open and frank prognostic discussion helps shaping a more realistic expectation of patients and caregivers. This can be followed with the discussion about the future priorities and preference of care. Instead of focusing only on diseasespecific management (e.g., dialysis decision), ACP adopts a more patient-center approach. ACP can reduce patients and caregivers' stress and anxiety, and improve their overall satisfaction. It also enhances shared understanding of relevant values and preferences amongst patients, family and healthcare providers (2).

be allowed to choose where (at home or stay in-patient) and

It has been difficult to engage transplant recipients to palliative care and integrate ACP to the post-transplant care process due to the impression that palliative care contradicts with the goal to receive transplantation (45). Despite a higher mortality risk in graft failure patients after resuming dialysis when compared to the transplant naïve patients, the decision of these graft failure patients may be influenced by his/her own past experience and experience of other patients (21,24). Some studies had demonstrated discrepancy in anticipated life expectancy between the patients and their clinicians. Patients commonly predicted better survival than their doctors (46). These factors would limit the effectiveness of ACP. Hence, clinicians have to communicate with patients and their family from time to time, and revisit the treatment goal related to care plan after graft failure, especially when condition of patients have changed or deteriorated (47).

Barriers to incorporate palliative care to kidney transplant management

The utility of palliative care among kidney transplant recipients remained lower than those transplant naïve patients with end stage kidney disease (ESKD) (27). A retrospective analysis of the United States national registry of patients with ESKD showed that ESKD patients who had ever been listed in transplant waitlist or received a transplant were more likely to receive intensive, in-patient end-of-life care. Kidney transplant candidates were also less likely to receive hospice service or discontinued dialysis before death (28).

There is a tendency among transplant recipients to opt for curative and more aggressive treatment until near the end of life. The disease courses of kidney transplant recipients are complex and highly variable. Some stable patients may experience rapid deterioration after an acute complication. Thus, the attending physicians may also have difficulty to identify appropriate timing for referral to palliative care (1). Furthermore, clinical ownership of patients and role ambiguity between transplant and palliative care team, misconception about palliative care among patients, caregivers and transplant teams are other barriers to incorporate early palliative care referral in kidney transplant care (1,37).

Lack of access to and resources in supporting nonmalignancy end-of-life care and organ failure patients would be another challenge. A pilot program of inpatient kidney palliative care for kidney transplant recipients with failing graft in United Kingdom resulted in increasing palliative care consultation from previously 5.9% to 24.1%, suggesting a genuine need of transplant palliative service and a significant gap in its provision to kidney transplant population (48).

Conclusions

The care needs of kidney transplant recipients with graft failure, especially those who are old and frail, need to be adequately addressed. Significant proportion of nephrology fellows reported insufficient training on basic palliative skills, such as treating pain, ACP and other aspects of endof-life care (49,50). Enhancing palliative skill education during nephrology and kidney transplant training would be useful to help nephrologists/transplant clinicians acquire the primary palliative skills and develop collaborative relationships with the palliative care team (51). Integrating palliative care principles into kidney transplant care can ensure treatment goals align with patients' expectations and improve their quality of life.

Further studies on the symptomology and various outcome measures (subjective and objective) would delineate the role of palliative care in kidney transplant management, facilitate evidence-based practice, and identify target patient groups for early palliative care intervention. Qualitative studies involving patients, caregivers and health care providers would also provide insight from the perspectives of various parties, and help aligning expectations and values.

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