RHODE ISLAND
MEDICAL JOURNAL


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Clinicians' Update: Kidney Transplantation in End-Stage Renal Disease (ESRD)

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Kidney transplantation remains the optimal treatment option for the management of end-stage renal disease (ESRD), providing a longer life span, a better quality of life, and lower healthcare costs compared with long-term dialysis treatment. Given recent encouraging developments in the field, this issue of the *Rhode Island Medical Journal* is devoted to discussing clinical topics in transplantation relevant to the entire medical community.

Ongoing improvements in graft and patient survival in both deceased donor and living donor kidney transplants are reported annually. According to the Scientific Registry of Transplant Recipients (SRTR), the 10-year all-cause graft failure rate declined to 51.6% for deceased donor recipients who underwent transplantation in 2006 compared to 57.2% for transplantations performed in 1998. Ten-year death-censored graft failure similarly declined from 33.7% to 26.2% during this period. Living donor recipients who underwent transplantation in 2006 experienced a 10-year all-cause and death-censored graft failure of 34.2% and 18%, respectively.

These superior outcomes have been attributed to several factors, including better organ procurement and preservation, more effective immunosuppressive medications and medication regimens and improved selection of both recipients and donors. Equally encouraging is that more transplants are being performed than ever, with the number of donors and transplants performed in 2019 in the United States reaching all-time highs, mostly due to increases in deceased donors. This has resulted in a decline in the number of patients waiting for a kidney transplant for the fourth year in a row. Nevertheless, the mismatch between organ need and supply remains severe, with the average wait time to receive an organ offer between 3–5 years at most centers and even longer in some regions of the country.

It is evident that kidney transplantation should be sought for all medically and psychosocially qualified patients with ESRD. Recently, former President Donald Trump signed an Executive Order entitled *Advancing American Kidney Health*, which calls for reform in the organ procurement and management system in the United States to significantly increase the supply of transplantable kidneys, with the goal of doubling the number of kidneys available for transplant by 2030. Additionally, the order encouraged the expanded support for living donors through compensation for costs such as lost wages and child-care expenses.

Rhode Island Hospital established its kidney transplant program in 1997 with the goal of providing convenient and quality services to our local community. We have since performed close to 1,500 kidney transplants, of which approximately 50% were derived through living donation. This success has required the active involvement of a wide range of healthcare specialists in a multidisciplinary approach. Our transplant team also emphasizes close consultation and cooperation with referring nephrologists and primary care physicians of transplant candidates as they progress from the initial evaluation to post-operative care and management. We hope this issue of RIMJ will help the Rhode Island medical community meet the ongoing challenges for patients with ESRD seeking successful kidney transplantation.

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Frailty and Kidney Transplantation

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ABSTRACT

Two significant policy changes, one in the way people are put forward for kidney transplants and the other in the way in which kidneys are distributed to people on the waiting list, make the question of whether someone is too frail to receive a transplant all the more relevant, particularly in Rhode Island. An executive order signed by President Donald Trump[1] stresses that efforts to treat kidney disease need to concentrate on providing more people with kidney transplants and increasing the number of organs transplanted rather than discarded. An effort to decrease waiting times for kidneys in large metropolitan areas[2] potentially means that younger, more desirable kidneys will be shipped out of New England, leaving longer waiting times and less desirable organs for transplantation in our region. The net effect of these changes may mean that potential older or more frail recipients could be faced with accepting kidneys from older or less desirable donors or spend more time on the waiting list and never receive a credible kidney offer. This raises the specter of poor outcomes from marginally functioning kidneys transplanted into marginally functioning recipients or increased rates of death on the waiting list. While organ allocation policies are beyond the ability of transplant nephrologists in Rhode Island to change, we will need to assess patients more closely for signs of frailty and work with referring doctors to reverse frailty when possible so that patients can take advantage of a kidney transplant even if the organ isn't ideal. This article will review the concept of frailty; how to asses it in general and in the context of a transplant evaluation; the risk of frailty in transplant outcomes and the benefits of transplant in reversing frailty; whether markers of frailty can be improved and whether that improves transplant outcomes.

KEYWORDS: kidney transplant, chronic kidney disease, frailty assessment, donor waitlists

INTRODUCTION

Chronic kidney disease is a growing worldwide problem and one from which the US is not immune. And while a functioning kidney transplant is seen as the ideal and ultimate renal replacement therapy, there is an overall shortage of organs compared to the number of people on the waiting list. The number of people waiting for a deceased donor kidney has decreased steadily from over 100,000 in 2014 to 92,906 at the start of 2018. Some 33,879 candidates were added to the list in 2018 while 34,591 were removed from the list. The ranks of those removed included 14,784 who received a deceased donor kidney transplant and 6,120 who received a living donor transplant. It also included 4,193 who died on the waitlist and 4,240 who were removed as too sick.[3] The decline in numbers on the waiting list reflects the effects of an earlier change in kidney allocation policies to help better match survival of the organ with expected survival of the recipient, decrease the number of organs discarded, and that backdated credit for waiting time to when a candidate initiated dialysis.[4]

In 2019, President Trump signed an executive order that sought to decrease the number of people receiving in-center hemodialysis and increase the number of people getting dialyzed at home and getting kidney transplants. The order envisioned an additional 17,000 kidney transplants.[5] More recently, efforts to reduce large disparities in waiting times around the country have led to changes in the way points are awarded that are used to determine one's standing on the list when an organ is offered. The net effect of this change is that organs that might have stayed in New England, where average wait times for a deceased donor kidney are around 5 years, would be transported to regions like New York, where wait times are closer to 10 years.[6] While the changes in kidney allocation will reduce waiting times in some regions, waiting times will increase in regions that become net exporters of kidneys. These changes raise the possibility that as older or more frail candidates move on to list, they will have to wait longer and will receive kidneys offers that reflect the diminished survival prospects of the recipient, or risk dying on the list before they are matched with a kidney.

To keep transplantation going in the region will require more careful evaluation of candidates as well as increased efforts to improve candidates' chances of surviving on the waiting list to receive an organ offer and thrive after

transplantation. The concept of frailty plays into this calculus. This paper will review the concept of frailty and address ways to assess it in general and as part of the transplant evaluation. The paper will look briefly at the risk to patient and transplant outcomes from frailty versus the potential benefit from transplant toward reversing frailty. The paper will examine potential ways to reverse elements of frailty to improve transplant prospects and whether such preconditioning works. The literature is vast, but this review will try to touch briefly on these important concepts.

FRAILTY

Frailty is often equated with old age or increased comorbidities. And while age and illness can factor into frailty, they are not substitutes for frailty. In their seminal paper on describing a frailty phenotype, Fried and colleagues wrote that frailty "may have a biological basis and be a distinct clinical syndrome"[7] and sought to develop a standardized definition. Using data from the Cardiovascular Health Study, they evaluated 5,317 men and women, including 582 Blacks, from 4 to 7 years of follow-up. They defined frailty as a clinical syndrome based on three or more of five characteristics: unintentional weight loss of 10 pounds or more in the previous year (shrinkage), self-reported exhaustion, weakness on a test of grip strength, slow walking speed over a set distance and low physical activity as defined on a standardized questionnaire.[8] In their study, frailty was associated with increased age, female gender, Black race, having a lower level of education and income, poorer health, and higher rates of chronic comorbid diseases and disability. They found that the frailty phenotype independently predicted falls, worsening mobility, hospitalization and death over three years. They defined intermediate frailty as having one or two of the characteristics, signaling an increased risk of becoming frail over 3–4 years. They defined frailty as a downwardly spiraling physiologic process of declining energy utilization and "loss of homeostatic capability to withstand stressors and resulting vulnerabilities." While they noted some overlap with disability and illness, they stressed that those concepts are not synonymous with frailty.

NEED TO ASSESS FRAILTY

There is a clear consensus, however, that frailty is a common feature of people with end-stage organ damage awaiting a transplant. The data also bear this out. According to a national study pooling data from three major centers, an estimated 16.4% of all kidney transplant candidates were considered frail between 2008 and 2018 while 14.3% of all kidney transplant recipients were considered frail during the same time.[9]

The American Society of Transplantation (AST) sponsored a consensus conference on frailty in February 2018 to standardize assessment of frailty in transplant candidates and generate ideas for further research.[10] In a survey of AST members concerned with kidney transplantation, 98.9% considered frailty in transplant candidates a risk factor for poor outcomes after transplantation, while 93.3% felt the need for a frailty score in making decisions on whether to transplant, and 67.1% thought age should be included in assessing frailty. Optimizing dialysis and volume status, nutrition, physical therapy and psychotherapy were thought essential components in improving frailty in patients with kidney disease awaiting transplant in the AST survey.

Much work has gone into looking at individual components of frailty, as well as association of age, comorbidities and frailty. Reviews on measuring frailty cite up to 75 functional assessment tools available currently, including questionnaires assessing physical capacity, tools like the Karnosky Performance Scale to assess physical performance, tools to quantify perceived frailty like the Fried's frailty phenotype (FFP), a frailty index of cumulative deficits, physical performance scores like walking speed, grip strength, ability to stand and balance, involuntary loss of muscle mass (sarcopenia), cardiopulmonary fitness testing to assess oxygen utilization.[11]

In a recent survey of US kidney transplant programs, McAdams-DeMarco and colleagues found the bulk of programs that responded to the survey (133/202) considered frailty a clinically relevant concept (99.2%) but only 96% said they thought frailty should be used in making decisions about whether someone was a transplant candidate. The survey found great heterogeneity in assessing frailty with respondents reporting that they used some 18 different tools to assess it. The most used test – by 19% of respondents – was a timed walk. Some 8% of respondents used the FFP while 8% used the Montreal Cognitive Assessment and 8% also used sarcopenia. Two-thirds of respondents said they used more than one test.[12]

Without a standardized method to assess frailty, clinicians often fall back on perceptions of frailty, which can be deceiving, with the consequence of potentially denying access to transplantation among those perceived as frail. Salter and colleagues looked at differences in perceived and measured frailty in 146 adults undergoing hemodialysis at a single dialysis unit in Baltimore.[13] Patient characteristics of frailty as perceived by nurse practitioners, nephrologists or patients were compared with measured assessment of frailty using the FFP. Older age and comorbidities were associated with a greater likelihood of being perceived as frail by nephrologists while women and non-African Americans were more likely perceived as frail by nurse practitioners. At the same time, of patients classified by the FFP as frail, only 42% were perceived as frail by nephrologists, 39.2% by NPs and 4.9% by patients themselves. The risk, according to the authors, was that older dialysis patients and women perceived as frail but not actually demonstrating frailty risked not being listed for transplantation.

And yet for frail patients, the risk of not being listed is significantly higher. In study of 7,078 transplant candidates between 2009–2018, frail patients were 38% less likely to be listed for transplant, regardless of age or other demographic factors. Frail Black kidney transplant candidates were 46% less likely to be listed than non-frail, non-Black candidates. They were 32% less likely to be transplanted compared to non-frail patients and they were 70% more likely to die on the waiting list.[14]

The relationship between aging, frailty and chronic kidney disease is central since aging increases the risk of poor outcomes from the cumulative burden of correlates for frailty like cognitive impairment, poly-pharmacy, disability, multiple comorbidities, malnutrition, and dialysis.[15] In the Rhode Island experience, the relationship between age and loss of kidney transplant and death after transplant was significant in patients who were inactive, smoked, had COPD, had peripheral vascular disease or required dialysis within a week after transplantation (delayed graft function).[16]

Age alone does not seem to define frailty in patients undergoing dialysis and transplantation and as a single entity, does not portend poorer outcomes. Researchers at Johns Hopkins, the University of Michigan and the University of California, San Francisco, pooled cohorts to compare frailty in subjects older than 65 and younger than 65 at three time points: within six months of starting dialysis; at time of kidney transplant evaluation; at time of admission for kidney transplant. Overall, frailty in all three time points was more prevalent in older patients who were also more likely to have slowness and weakness. Younger subjects were more likely to experience exhaustion in all three time points. The authors concluded that while frailty was more prevalent in older subjects, younger subjects still had a high burden.[17] A registry-based study at Oslo Hospital of all potential kidney transplant recipients age 65 or older who received a deceased donor kidney transplant between 2000 and 2014 found no difference in outcomes between those who received a first kidney and those who received a second kidney re-transplant. Five-year survival censored for death with a functioning graft in those receiving a second transplant was 88% versus 90% for those receiving a first transplant (P = 0.475%).[18] Risk factors for increased chance of death with a functioning graft also included longer time on the waiting list before re-transplantation, although the authors noted that overall waiting time at their center was small such that their findings might be even more applicable at centers with longer waiting times.

FRAILTY WHILE WAITING

The risk of death on the waiting list for frail patients has led to much thought about whether chances to receive a kidney can be enhanced by "preconditioning" of frail candidates to improve physical stamina. Researchers at the Mayo Clinic identified what they described as high-risk kidney transplant patients (59 years or older, diabetes and or more than three years on dialysis) and evaluated them using the FFP and Short Physical Performance Battery. They found that both frailty and physical performance were significantly associated with death on the waiting list (hazard ratio 6.7, 95% confidence interval 1.5–30.1; P=0.01). They also found that the relationship between frailty, physical performance score and death on the waiting list were independent of age, diabetes or length of time of dialysis.[19]

Time on the waiting list can also increase frailty, such that some suggest measuring changes in frailty over the course of time between listing and transplantation. Researchers at Johns Hopkins noted that 22% of 569 kidney transplant candidates enrolled in their cohort study of frailty became increasingly frail while 24% became less so. While Black race was associated with becoming less frail and diabetes was associated with remaining stably frail, the longer candidates remained on dialysis, the less likely they were to become less frail. Given the dynamic change in frailty in some patients, these researchers recommended assessing frailty at the time of listing and time of transplantation since candidates who became more frail faced longer hospitalization times post-transplant as well as a higher risk of mortality post-transplant.[20] Researchers at Columbia University used a timed "get up and go" test for patients on the waiting list to see if that might predict outcomes after transplant. In the end, participants in the study who were transplanted had shorter times on the test than those who remained on the waitlist. However, there was no association between test time and probability of removal from the waitlist or prolonged hospitalization after transplantation or 30-day readmissions.[21]

In an ongoing trial, a group of Canadian researchers hopes to better evaluate whether frailty is associated with death on the waitlist, withdrawal from the waitlist as well as whether frailty is associated with hospitalization, quality of life and even being listed. Their plan is to evaluate potential candidates using the FFP, the frailty index, the Short Physical Performance Battery and the Clinical Frailty Scale (CFS) at the time of initial evaluation for listing and annually after that. The goal is to understand the association of frailty and outcomes from patient on the waitlist before incorporating measurement of frailty into the regular waitlist workup.[22]

The association between waitlist mortality and frailty is not clear. The CFS, a validated instrument in dialysis patients, uses overall clinical impression to award a single point for each degree of perceived frailty. In a cohort of incident dialysis patients assessed between 2009 and 2013, each point increase in the CFS was associated with an increase in the hazard ratio of death (HR 1.22; 95% CI, 1.04–1.43; P=0.02).[23] In a separate multi-center study, researchers assessed whether an association existed between frailty on the waitlist and accumulated burden of comorbidities as

assessed by the Charlson Comorbidity Index. In a study of 2,086 candidates on the kidney transplant waitlist, 18.1% were frail and 51% had a high comorbidity burden. They found that among non-frail patients, a high comorbidity score was associated with a statistically significant risk of mortality (HR 1.66 95% CI 1.17–2.35). But among frail patients, high burden of comorbid conditions did not show an association with mortality. Stratified by age, the higher comorbidity index portended worse mortality in patients waiting for kidney transplantation who were under 65, while a high burden of comorbidities was not associated with waitlist mortality in patients age 65 and greater on the waitlist.[24]

INTERVENTIONS

The question then becomes whether one can intervene with frail candidates to improve their survival on the waitlist, their chances of getting a kidney and survival after transplantation. Part of the problem in increasing exercise tolerance among kidney transplant candidates is that people enter the waitlist already in poor physical shape. According to one study, 95% of new starts on dialysis have physical fitness levels below the 20th percentile for the general population, and just over half (56.4%) are able to walk one block, 23.8% can climb 24 stairs, and only 18.5% said they could walk a mile.[25] Researchers at several centers are looking into adapting an exercise module developed by the American College of Sports Medicine to create an exercise module for people transitioning to dialysis. The idea is to develop a practical and cost-effective package to help patients starting dialysis overcome barriers to exercise.[26]

Researchers at the Mayo Clinic used supervised exercise sessions in frail patients with stage IV chronic kidney disease or greater to see whether their intervention could improve strength. They enrolled 21 patients in two supervised outpatient exercise sessions per week for eight weeks. The intervention, which included strength, endurance and flexibility training, led to improvement in frailty parameters like walk speed, grip strength and fatigue, although none of the changes were statistically significant. Scores on the Short Physical Performance Battery did improve significantly. The authors suggest that their results are encouraging and warrant evaluation in a larger, multi-site study.[27]

The transplant clinic at Stanford University began doing physical assessments of transplant candidates once their accumulated waiting time put them in the top of the center's waitlist. Rather than assessing frailty, the clinic assessed 60 second sit-to-stand and 6-minute walk tests. They found that the lower the scores on the two tests, the higher risk of removal from the waitlist or death on the waitlist.[28]

FRAILTY AFTER TRANSPLANT

Does transplantation improve frailty among kidney recipients? Again, the data appear mixed. Researchers in the Netherlands studied 176 kidney transplant recipients at their center in Groningen between 2015 and 2017 and followed for up to three years. Using their own frailty scale (Groningen Frailty Indicator), they found that 34 non-frail patients became frail after transplantation, 125 patients remained unchanged, and 19 frail patients were no longer frail. The GFI includes 15 questions in eight functional domains including mobility, vision, hearing, nutrition, comorbidities, cognition, psychosocial functioning and physical fitness. Changes in cognition and psychosocial functioning contributed most to the shift from not frail to frail after transplantation.[29] In contrast, researchers at Johns Hopkins and the University of Michigan assessed frailty using the FFP and then examined changes in health-related quality of life (HRQOL) in 443 kidney transplant patients at their centers between 2014 and 2017 for three months post-transplant. At the time of transplant, frail patients had worse HRQOL scores than non-frail patients, but both groups showed improvement one month post-transplant. At three months, frail transplant recipients had statistically significant continued improvement in physical HRQOL but non-frail patents did not. The same held true for changes in mental HRQOL. Both frail and non-frail transplant recipients reported improvement in kidney disease specific HRQOL.[30]

CONCLUSION

The topic of frailty in chronic kidney disease and transplantation remains in flux. The transplant community knows that frailty is a poor indicator for outcomes in transplantation. Frailty can affect not only if patient can get transplanted once placed on the waitlist but also whether that person can even get on the list to begin with. As older people undergo transplant evaluation and face the prospect of only getting offers of kidneys from more marginal donors, assessing candidates for frailty and finding ways to reverse the components of frailty that are amenable to improvement becomes all the more important. However, the transplant community remains divided on the best tool(s) to use to make the assessment and whether exercise conditioning can help give people more strength, stamina and improve energy metabolism. The Organ Procurement and Transplantation Network (OPTN) has temporarily put on hold the implementation of changes in the kidney allocation system while the Department of Health and Human Services reviews concerns about the changes that were submitted just before the new rules were due to take effect December 15, 2020. Whatever the outcome of that review, efforts to improve a transplant candidate's conditioning and stamina could also be important tools in improving access to and survival after kidney transplantation.

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Management of Cardiovascular Risk Factors in Dialysis-Dependent End Stage Kidney Disease

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KEYWORDS: chronic kidney disease (CKD), management of CVD risk factors, renal replacement therapy (RRT), end stage kidney disease (ESKD)

INTRODUCTION

Over nineteen million patients face progressive chronic kidney disease (CKD) in the United States.[1] The preferred treatment with proven clinical outcomes for end stage kidney disease (ESKD) patients remains kidney transplantation. Unfortunately, the number of kidney transplants has reached a plateau in recent years with a simultaneous increase in the number of patients awaiting transplantation and the length of time they wait.[2] For the majority of these patients, renal replacement therapy is the initial treatment while they await transplantation, during which time they face many barriers. One medical barrier is cardiovascular disease (CVD), which is reported to be 20 times higher than the general population, accounting for 40% of deaths of US dialysis patients.[3] By comparison, a 30-year-old dialysis patient bears nearly the same risk as an 80-year-old non-dialysis patient for CVD-related death.[4] The complete etiology of the increased risk of CVD is not fully understood and is likely a combination of both traditional and novel risks factors. The traditional risk factors include non-modifiable (age and sex) and modifiable (dyslipidemia, diabetes, smoking, and hypertension) components. This review will discuss ways to address the latter modifiable risk factors.

Identification of high risk individuals with the use of assessment tools such the Framingham Risk Score (FRS-CVD) and the ASCVD (American Heart Association (AHA)/ American College of Cardiology (ACC) 2013) have been validated in the general population, provide guidance on optimal therapy for primary prevention using lifestyle modifications and pharmacological interventions.[5] While proposals are ongoing for the addition of renal function to current scores or developing new scores, the current use of these tools in CKD and ESKD patients has limited applicability.[6–9] The Pan American Health Organization/World Health Organization (PAHO/WHO) has developed a calculator that includes glomerular filtration rate (GFR) but further studies are needed to assess its applicability.[10] Even without the use of these tools, evidence has established that decreasing GFR increases CVD and mortality.[11–14] Proposed novel risk factors that may be contributing to this higher incidence of mortality and CVD unique to CKD and ESKD population include anemia, volume status, mineral metabolism, electrolyte disarray, albuminuria, uremia and inflammation.[15–17]

DYSLIPIDEMIA

Dyslipidemia in the general population is characterized by elevated low density lipoprotein (LDL) which is oxidized to form atherosclerotic plaques. In contrast, ESKD patients also develop hypertriglyceridemia, a decrease in high density lipoprotein cholesterol (HDL-C), an accumulation of apolipoprotein B (Apo B) containing lipoproteins, and increased concentrations of lipoprotein(a) particles.[18,19] All lipid classes are affected. One hypothesis is that as CKD progresses, so does uremia and oxidative stress. This causes post-translation protein modification of both LDL and HDL through glycation, oxidation and carbamylation, resulting in both a decrease in the quantity and quality of their function.[20–22] This hypothesis may explain why statins have not been beneficial in this population.

The mainstay of guideline therapy has been the use of statins to reduce LDL levels in the general population and in CKD patients.[23] Unfortunately these guidelines do not include ESKD patients due to lack of robust evidence. The SHARP study showed a 17% proportional reduction in major atherosclerotic events in 3,023 patients on dialysis who were randomized to receive simvastatin plus ezetimibe vs placebo during a 4.9 year follow-up period.[24] The 4-D trial and the AURORA did not reflect the same outcome, and showed there was no significant difference in either the placebo or intervention group. The current Kidney Disease Improving Global Outcomes (KDIGO) and ACC/AHA guidelines do not support the initiation of statins in ESKD. KDIGO recommends statins for all patients with CKD not on RRT and who are at least 50 years old. For adults 18 to 49 years old who have CKD, statins are recommended if there is a history of coronary artery disease, diabetes mellitus, stroke, or an ASCVD risk > 10%. Statins when initiated prior to dialysis can be continued, as there are no recommendations on discontinuation.[25] Extrapolating from hemodialysis patients, International Society for Peritoneal Dialysis (ISPD) guidelines refers to KDIGO for dyslipidemia management in peritoneal dialysis patients (PD).[26,27]

While statins have become the cornerstone, the latest discovery for dyslipidemia treatment is monoclonal antibodies. Currently, evolocumab and alirocumab are the available proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors. PCSK-9 binds to hepatocyte receptors and promotes increased LDL levels.[28] Inhibition of this protein by evolocumab has shown reduction of LDL levels by 59% and a reduction in cardiovascular events.[28] Unfortunately there is limited data on safety and efficacy in CKD patients and ESKD patients have been excluded from trials so there is a paucity of guidance for use in this patient population.[29–31]

Eicosapentaenoic acid (EPA) or omega-3 fatty acids decrease pro-inflammatory cytokines, interleukin-6 and leukotriene B4 by inhibiting the activation of their gene production.[32] The ACC/AHA guidelines do include recommendations for fish intake twice a week and use of omega-3 fatty acids in hypertriglyceridemia. In ESKD patients, omega-3 fatty acids have been studied for an effect on arterio-venous fistula patency with unfortunately no clear benefit established.[25] However, in a small study by Lok, 99 out of 196 ESKD patients who were randomized to receive the supplement demonstrated superior cardiovascular event-free survival in the fish oil group (HR 0.43 [95% CI, 0.19 to 0.96], p = 0.035) and a 7.74 point reduction in systolic BP.[33] Fish oil is generally well tolerated with the major side effects being gastrointestinal from belching or flatulence, and taste perversion. Nevertheless, use in ESKD patients should be individualized.[34]

ASPIRIN

There has been a change in the use of aspirin as primary prevention in the general population as new data has shown less benefit. Recent guidelines recommend patients with high calculated CVD risk scores based on traditional factors to initiate therapy.[35]

Unfortunately, this may not be applicable to ESKD patients since there is limited data on mortality benefit. Analysis of hemodialysis patients receiving aspirin prescriptions in the DOPPS study demonstrated that an aspirin prescription was associated with an increase in myocardial infarction and any cardiac event. [36] In a meta-analysis evaluating CKD and use of anti-platelet therapy, there was no clear effect of antiplatelet therapy on the risk of cardiovascular death (OR, 0.91; 95% CI, 0.67–1.13; I^2 = 0%) or all-cause death (OR, 0.87; 95% CI, 0.71–1.01; I^2 = 0.8%) compared with placebo or usual-care control groups in 27,773 participants from 50 trials.[36] They did show that for every 1,000 people with CKD treated, 23 patients would avoid major cardiovascular events but 9 patients would have a major bleeding episode and 35 would have minor bleeding episodes. At this time there is no recommendation to initiate aspirin therapy for primary prevention in ESKD patients.

SMOKING CESSATION

Smoking continues to challenge both the general and kidney disease populations. It remains the leading cause of preventable death in the United States. While specific data in dialysis patients is lacking, cessation is likely to reduce cardiovascular disease and mortality. Similar strategies involving nicotine replacement therapy can be utilized as well as drug therapy such bupropion and varenicline, with varenicline requiring renal dosing. [35]

DIABETES MANAGEMENT

Glycemic control involving dietary modifications, exercise, metformin, SGLT-2 inhibitors and GLP-1R agonists with a target hemoglobin A1C (HbA1C) of < 7% has shown CVD and mortality benefit in type 2 diabetic patients in the general population.[37] KDIGO recommends all type 2 diabetic patients with GFR greater than 30 (CKD stages 1-3) be treated with metformin, sodium–glucose cotransporter-2 (SGLT-2) inhibitors with the addition of lifestyle modifications (physical activity, nutrition and weight loss) to reach a target HbA1c of less than 6.5% or 7%.[38] Unfortunately the accuracy of HbA1c measurements in dialysis patients is unclear but without an alternative and wide use in clinical trials, it remains the marker of choice.[39] After initiation of first-line treatments, additional oral agents will require dose adjustment based on renal function and individualized to the patient.[39] The lack of data for HbA1c targets in dialysis patients poses an exceptional challenge for management in dialysis dependent diabetic patients.[39] As all cause mortality and CVD outcomes are worse in patients with poor glycemic and these patients are to be evaluated for transplantation, it is reasonable to provide targeted glycemic control based on observational data. [37,40–43]

HYPERTENSION

Deciphering the various definitions and recommendations for hypertension between guidelines from different societies can add to the complexity of treating this patient population. While all seem to agree that elevated blood pressure increases CVD and mortality, blood pressure thresholds and targets for different groups remains an area of debate.[44–46] Blood pressure readings can be taken in office, at home and continuously with an ambulatory pressure monitoring (ABPM) device. The 2017 ACC/AHA guidelines defines hypertension as an office systolic blood pressure greater than 130 mmHg or diastolic blood pressure of greater than 80 mmHg, while the 2018 ESC/ESH guidelines uses an office systolic blood pressure of greater than 140 mmHg and/or diastolic blood pressure of greater than 90 mmHg.[47–49] In the ground breaking SPRINT trial, diagnosis of hypertension was based on automated cuff readings in an office setting.[50] The National Institutes of Health and Care Excellence

(NICE) recommends confirming an elevated office reading with an ABPM daytime average or home blood pressure average of 135/85 mmHg or higher while the European Society of Cardiology/European Society of Hypertension (ESC/ESH) accepts an average ABPM of greater than 130/80 mmHg to be hypertensive.[47,48]

Once the hurdle of diagnosis has been achieved, the complexity continues in target goals and recommendations on the initial pharmacological regimen. Counseling on lifestyle modifications such as smoking, diet and exercise is recommended by the majority of the guidelines at initiation of treatment.[44,45,47–49] In both the diabetic and non-diabetic adult CKD population, KDIGO stratifies blood pressure targets based on albuminuria. When urine albumin excretion is less than 30mg/24hours the suggested targets are: systolic blood pressure of less than 140 mmHg and diastolic blood pressure of less than 90 mmHg. When albumin excretion is greater than 30mg/ 24hours, the recommended targets are: systolic blood pressure of less than 130 mmHg and diastolic blood pressure of less than 80 mmHg.[51] Angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), beta-blockers and diuretics are effective in the treatment of hypertension. Initial choice of medication should be individualized. In patients with diabetes, CKD, and albuminuria, ACEis and ARBs should be considered first as renin angiotensin aldosterone system (RAAS) blockade has shown benefit in reducing albuminuria and preventing CVD events.[52,53] Additional therapy should be individualized based on side effects, patient characteristics and co-morbidities.

Unique to dialysis patients is that blood pressure readings can vary when taken pre-, inter- and post-dialysis treatments in addition to in-dialysis unit, office and home locations.[54,55] The relation between the various readings has shown a stronger association of home or out of center BP readings with CVD and mortality.[56,57] The European Renal and Cardiovascular Medicine (EURECA-m)/European Renal Association–European Dialysis and Transplant Association (ERA-EDTA)/ ESH consider home or ABPM values of ≥135/85 mmHg on non-dialysis days and average BP≥130/80 mmHg over 24-hours respectively for hemodialysis patients and an office BP≥140/90 for PD patients to be diagnostic of hypertension.[58] The Kidney Disease Outcomes Quality Initiative (KDOQI) made a grade C recommendation for a pre-dialysis blood pressure target of less than 140/90 mmHg and post-dialysis blood pressure target of less than 130/80 mmHg.[59]

The pathophysiology of hypertension in dialysis-dependent ESKD patients is multifactorial. Proposed factors include salt and volume retention, RAAS and endothelial cell dysfunction, sleep apnea and use of erythropoietin agents.[53,60,61] A low sodium diet (2 grams per day) is recommended.[59] An attempt to optimize volume removal with aggressive ultrafiltration during hemodialysis has been shown to improve hypertensive control.[62] Data from meta-analysis suggests the use of pharmacological therapy is associated with CVD reduction and survival benefit.[63,64] While ACEi have shown efficacy in decreasing left ventricular mass as well as providing RAAS blockade, use may be limited due to side effects.[58,61] Multiple agents will mostly likely be required and should be individualized to each patient. Patients maintained on PD have also been shown to be chronically volume overloaded as evidenced by elevated atrial natriuretic peptide levels and left atrial volume by echocardiography. In general, this is managed by increasing the glucose concentration in the dialysate to promote a higher osmotic gradient to promote better ultrafiltration. However, a high peritoneal dialysate glucose concentration (PDGC) may induce metabolic syndrome, which has been associated with a higher CVD mortality in PD patients.[58,65] Further data on blood pressure targets and pharmacological regimens is lacking in PD patients.

Due to the lack of evidence from quality randomized controlled trials or strong recommendations from society guidelines, hypertension treatment in advanced CKD (stage 5) and dialysis-dependent ESKD is based on observational data and expert opinion.[46,63,64] Unfortunately, the lack of clarity on this issue most affects patients who are awaiting imminent transplantation, limiting the optimization of their medical management.

SUMMARY

This summary provides guidelines based on the limited available data in this vulnerable patient population. Given the high burden of CVD in the ESKD population and the multiple challenges these patients face, providing a multi-disciplinary approach to mitigate cardiovascular risks may result in improved clinical outcomes and benefit these patients while they wait on the long road to transplantation.

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Malignancy After Renal Transplantation: A Review

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KEYWORDS: renal transplantation, end-stage kidney disease, post-transplant malignancy, cancer screening in post-transplant renal recipients

INTRODUCTION

Renal transplantation provides a significant mortality benefit to patients with End-Stage Kidney Disease (ESKD) compared to those remaining on renal replacement therapy (RRT), with many centers reporting one-year graft survival rates of 95%.[1] The increase in allograft "half-life" is seen with both living donor kidney transplants (LDKT) and deceased donor kidney transplants (DDKT), and correlate to advances in immunosuppression options.[2] As kidney transplant recipients are living longer, careful monitoring for associated complications such as post-transplant malignancy is necessary. Post-transplant malignancy is the third most common cause of death in renal transplant recipients, with some malignancies occurring at much higher rates compared to the general population.[3] Immunosuppressant medication as well as oncogenic viruses seem to play a major role in malignancy development. This review will discuss malignancy after renal transplantation and offer an approach to caring for these patients.

EPIDEMIOLOGY

When to Suspect Malignancy

Renal transplant recipients have at least a 3- to 5-fold increase in malignancy incidence compared to the general population. This increased risk is much more significant for specific malignancies such as non-melanoma skin cancer (NMSC), while some other more common cancers such as prostate and lung cancers occur at approximately the same rate in transplant patients.[1,3] Several donor and recipient factors play an important role in malignancy development. ESKD itself appears to be oncogenic for the development of renal malignancy, with standardized incidence ratios (SIR) of 1.42 compared to age-matched cohorts without ESKD.[4] This is attributed to the development of acquired cystic kidney disease in this patient population, which markedly increases the risk of developing malignancy in these senescent organs.[5] Time spent on dialysis before transplantation has also been identified as a risk factor for developing post-transplant malignancy. Pre-transplant malignancy in either the donor or recipient, as well as susceptibility to various oncogenic viruses also contribute this risk. Differences in the donor type of transplant are associated with varying malignancy risk. Recipients of living-donor kidneys are at lower risk of cancer overall, particularly for genitourinary cancer and post-transplant lymphoproliferative disorder (PTLD).[6]

Undoubtedly the most important factor in post-transplant malignancy occurrence is prolonged exposure to immunosuppression – medications required to prevent the transplanted kidney from rejection. Immunosuppressants impair the body's immune surveillance of oncogenic mutations which would terminate such sequences under normal circumstances. Although improvements in immunosuppressive therapy has resulted in improvements in long-term graft survival, longer exposure is associated with a higher rate of de novo malignancy in transplant recipients.[1]

In the US, the risk of developing NMSC after renal transplantation is more than 20-fold higher than that of the general population. The other commonly encountered post-transplant malignancies are those influenced by oncogenic viruses (**Table 1**). Some of the more familiar malignancies in the general population such as breast, prostate, lung, uterine and pancreatic cancers tend to occur at about the same rate (or slightly less frequent) in kidney transplant recipients. Other more common malignancies such as colon, bladder and esophageal cancers occur at a rate approximately 2–5 times higher in transplant patients.[3]

Table 1. Viruses commonly associated with malignancy after renal transplantation. *Adapted from Morath C, Mueller M, Goldschmidt H, Schwenger V, Opelz G, Zeier M. Malignancy in renal transplantation. J Am Soc Nephrol. 2004;15(6):1582-8.*

Virus	Malignancy Type
Epstein-Barr Virus (EBV)	Post-Transplant Lymphoproliferative Disorder (PTLD)
Human Herpesvirus 8 (HHV-8)	Kaposi's Sarcoma
Human Papillomavirus (HPV)	Cervical Cancer Vulvar Cancer Penile Cancer Skin and Tonsillar Cancer
Hepatitus C Virus (HCV), Hepatitus B Virus (HBV)	Hepatocellular Carcinoma (HCC)

Transplant recipients should be monitored closely for the development of de novo malignancy throughout their entire post-transplant course, but as alluded to previously, malignancy risk increases with duration of follow-up. The risk of any malignancy after 10 years of renal transplantation is reported to be almost 14-fold higher than the general population, compared to much lower rates at 1- and 3-years post-transplant.

PATHOGENESIS

Immunosuppression Regimen/Host Factors/Viral Causes

Several factors contributing to post-transplant malignancy development have been identified including patient age, sun exposure, previous malignancy, concomitant viral infection, the type and intensity of immunosuppression and duration of dialysis pre-transplant. The effect of the intensity of immunosuppression on malignancy development is demonstrated across the various solid organ transplants and their post-transplant malignancy rates. Heart and lung transplant recipients require higher levels of immunosuppression than their kidney counterparts, and this is associated with a higher incidence of malignancy.[7] Immunosuppression intensity as an independent risk factor for post-transplant malignancy is also supported by studies comparing higher vs lower cyclosporine trough levels, with a 12% reduced incidence in the latter group.[8]

In the "modern era" of immunosuppression, anti-rejection regimens have been more customized to the individual recipient, based on the perceived risk for rejection. It is now recognized that the development of alloantibodies directed against the graft has a significant adverse impact on allograft survival and the previous practice of reducing the intensity of immunosuppression among transplant recipients of older vintage is no longer standardly applied. Although this practice may ultimately improve long-term allograft outcomes, there is an associated increase in malignancy incidence attributed to heightened immunosuppression exposure.

The type of immunosuppression used may also influence the risk of malignancy in the post-transplant setting. Lim et al. demonstrated that the risk for malignancy after first kidney transplantation was significantly higher in patients treated with T cell–depleting antibodies for treatment of acute rejection compared with those recipients not experiencing acute rejection, with most confined to the genitourinary tract.[9] Similarly, T cell depletion using anti-thymocyte globulin as induction therapy has also been associated with higher rates of post-transplant lymphoproliferative disease (PTLD) compared to less intense regimens (e.g., anti-IL-2 receptor antibodies). Furthermore, calcineurin inhibitors (CNIs) such as tacrolimus and cyclosporine raise transforming growth factor (TGF-β) levels which may promote tumor growth.[1] However, not all immunosuppressants are considered oncogenic. Mammalian target of rapamycin (mTOR) inhibitors, including sirolimus and everolimus, may have anti-neoplastic properties and inhibit angiogenesis of tumor cells.[10] More information is needed to make more definitive conclusions regarding mTOR inhibitors and malignancy risk, as one meta-analysis suggests a decrease in NMSC but an increased risk in prostate cancer.[11]

Immunosuppression itself impairs the host's ability to survey the immune system for potentially hazardous mutations. This is perhaps best demonstrated in the higher incidence of post-transplant skin cancers (specifically NMSC) and viral-related malignancies. It is well known that sun exposure predisposes the host to carcinogens, which can eventually lead to skin cancer. The immune system is responsible for identifying mutations associated with carcinogen exposure and terminating them prior to malignancy development. Without inhibitory checkpoints in place, malignancy develops at much higher rates. Several viruses are associated with malignancy in immunocompromised hosts (**Table 1**). The viruses encode oncogenic proteins to promote malignancy development.[12] In immunocompetent individuals the viruses do not cause significant illness and remain dormant. However, the virus activity is unopposed in immunosuppressed individuals, and malignancy may subsequently occur.

Donor factors such as the unknowing donation of neoplastic cells at the time of transplantation are possible, but more commonly, malignancy occurs de novo in the recipient. Host factors play an important role in this risk. For example, the incidence of renal cell carcinoma (RCC) in kidney transplant recipients is influenced by male sex, increasing age, African ancestry, acquired cystic kidney disease, and the longer duration on dialysis. The underlying etiology of ESKD can also play a role, as evidenced by the increased of RCC in patients with tuberous sclerosis. Glomerulonephritis (GN) accounts for approximately 10% of the ESKD population in developed countries. Many of these disease states require immunosuppression as part of the treatment regimen, some of which may be potentially oncogenic (e.g., cyclophosphamide). Exposure to such medications may double the risk of post-transplant malignancy compared to other allograft recipients and should therefore be well-documented in patient records.[14]

SKIN CANCERS

Skin cancers are by far the most common post-transplant malignancy, accounting for approximately 40% of cases.[2] Patients with fair complexion are at greatest risk, and rates increase with prolonged sun exposure and geographic location. In Australia, for example, the cumulative risk of skin cancer post-transplant is as high as 45% at 11 years and 70% at 20 years.[3] The risk of melanoma is 3–4 times higher in renal transplant recipients, but the non-melanoma skin cancers (NMSC) are far more common. These NMSC include

basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and Kaposi's sarcoma. Kasiske et al demonstrated that cumulative incidence of NMSC was 0.3%, 0.9%, 2.3%, 5.0%, and 7.4% at months 3, 6, 12, 24, and 36 months respectively.[15] BCC and SCC are responsible for > 90% of skin cancers post-transplant. Although NMSC is not considered as aggressive as some other malignancies, SCC in transplant patients carries a 3-year mortality rate of 46% for metastatic disease and recurrence is common.[16] Skin surveillance and ultraviolet (UV) protection is strongly recommended in the post-transplant period. CNIs such as tacrolimus and cyclosporine are highly associated with NMSC post-transplant and those experiencing recurrent skin cancers typically are frequently converted to alternative regimens such as mTOR inhibitors to mitigate this risk.[17] Once identified, the risk of skin cancer recurrence is high, and the clinician should emphasize the importance of skin surveillance and protection post-transplant.

Kaposi's sarcoma (KS) is an angioproliferative cutaneous cancer caused by human herpesvirus 8 (HHV-8) in immunocompromised hosts. They are purple-red-bluish lesions presenting as non-painful, non-pruritic, macules, papules or nodules. The incidence of KS is greatly increased in renal transplant recipients, particularly in certain ethnic groups occurring in up to 5% of transplant patients.[18] KS is more strongly associated with CNIs than other immunosuppressants. Visceral involvement of the GI tract or other mucosal surfaces is possible but less common, and outcomes are variable. Approximately one-third of patients achieve complete remission with altering immunosuppression therapy, but another one-third of patients die at 3 years after diagnosis.[3]

POST-TRANSPLANT LYMPHOPROLIFERATIVE DISEASE (PTLD)

PTLD includes several lymphoid disorders such as lymphomas (both Hodgkin and NHL), lymphoid leukemias and multiple myeloma. The World Health Organization (WHO) classifies PTLD into four categories: early lesions, polymorphic, monomorphic, and classical Hodgkin's lymphoma (cHL). PTLD has an incidence rate of 1.8% at 10-years post-transplant and is more common in pediatric transplant recipients. It is typically associated with Epstein-Barr Virus (EBV) infection, which chronically infects B-cells and leads to their proliferation. Immunosuppression inhibits T-cell regulation of the EBV-infected B cells, and uncontrolled proliferation may ensue.[19] The risk of PTLD is highest when an EBV (–) patient receives a kidney from an EBV (+) donor.

Although PTLD can occur at any time post-transplant, Non-Hodgkin Lymphoma tends to be the most aggressive and can occur within the first year after transplant when immunosuppression is highest and there is more risk for viral infection. More recent data suggests the interval to disease onset is increasing to later in the post-transplant course at 48–81 months.[20] The lymphoid proliferations can be localized to lymph nodes or disseminated (extra-nodal) to involve the transplanted organ, or other native organs such as the central nervous system (CNS). In kidney transplant patients, the most common location for PTLD involves the gastrointestinal tract. Clinical presentation is highly variable and may include lymphadenopathy, night sweats, weight loss or chills. Treatment includes reduction of immunosuppression, and often a B-cell directed chemotherapy regimen. However, there is no consensus on how immunosuppression should be adjusted.

ANOGENITAL CANCERS

Anogenital malignant neoplasms occur with a 14- to 50-fold increased incidence in kidney transplant patients and human papilloma virus (HPV) infection plays a major role in the development of such cancers. These include cervical, vulvar, vaginal, penile and anal malignancies. [21] The incidence of HPV infections in kidney transplant recipients is 17% to 45%, with a low rate of cytologic alterations found on pap testing.[22,23] Vulvar and vaginal cancers are the least common gynecologic cancers in the general population. Like cervical cancer, most vulvar cancers after transplantation are HPV-related with the high-risk HPV types playing the major role in the pathogenesis. Among kidney transplant patients, a younger age at transplantation (18–34yo) is associated with increased risk of cervical cancer whereas vulvar cancer is more likely to occur at 5 or more years after transplantation.[24]

The choice, duration and intensity of immunosuppressive agents may influence the incidence of gynecological cancer development; however, studies on the direct effect of specific immunosuppressants on gynecologic cancers are sparse and conflicting. One hypothesis suggests immunosuppression may contribute to reactivation of latent HPV infections, including high-risk oncogenic HPV types.[25] A US study of 187,649 solid organ transplant recipients (64% renal transplant), did not report an increase in invasive cervical cancers after transplantation, although it noted an increase of in situ carcinoma; this may be explained by very close follow-up due to chronic immunosuppression and subsequent earlier detection of noninvasive cervical lesions. Decisions regarding whether to withdraw or reduce immunosuppression after a gynecologic cancer in the post-transplant population should be individualized.

OTHER CANCERS AND THOSE WITHOUT INCREASED RISK

Other malignancies after renal transplantation occur at varying rates. Some of the more commonly encountered cancers in the general population (breast, prostate, lung, pancreas and uterine) occur at about the same rates in renal transplant

Table 2. Standard Incidence Ratios (SIRs) of various malignancies after renal transplantation compared to the general population.

Standard Incidence Ratio (SIR)	> 20x	10–20x	2–5x	1–2x
Type of Cancer	NMSC Lip Cancer Oropharyngeal Kaposi Sarcoma	Cervical Vulvar Lymphoma Renal and Ureter Bladder Thyroid Neuroendocrine	Colorectal Melanoma	Prostate Lung Pancreas Breast Uterine

recipients. Colon cancer is encountered at a slightly higher rate in transplant patients, 2–5 times the general population. Finally, urologic malignancies including the bladder, ureters and kidneys occur at rates 5–20 times higher in renal transplant recipients.[15] **Table 2** contains a more comprehensive list of malignancies and their standardized incidence ratios (SIRs) after renal transplantation.

PREVENTION

Post-Transplant Cancer Screening Guidelines

Although the increased risk of malignancy after renal transplant is well established, there is little evidence to support screening guidelines in this complex patient population. [26] As one might expect, the guidelines are adopted from those used for the general population as well as for those cancers seemingly unique to renal transplant recipients. For malignancies already associated with cancer screening guidelines in the general population, many societies suggest utilizing the same approach in renal transplant recipients. This includes colon, breast, and prostate cancers. Lung cancer screening is recommended *against* by the American Society of Transplantation (AST) in renal transplant recipients, as is the case for renal and other urologic cancers despite their increased incidence in the transplant population.[27] Skin cancer screening with self-examination and annual dermatology surveillance for highest-risk transplant patients is recommended, and risk stratification tools exist to aid the clinician in identifying these individuals.[28] Despite these recommendations, evidence is lacking to support changes in outcomes.

Cervical cancer is the only gynecologic cancer for which there are effective screening tests for the general population to detect more treatable precancerous lesions. The American College of Obstetricians and Gynecologists and AST recommended more frequent, annual screening for cervical cancer in renal transplant recipients. Still some other societies recommend pap testing with pelvic examination every 3 years, which is in line with the general population guidelines.[29] Screening for PTLD/lymphomas are recommended against by most societies, and hepatocellular carcinoma (HCC) screening with abdominal ultrasound is only recommended in transplant patients with compensated cirrhosis.

A lack of supporting evidence is not the only limitation of cancer screening in renal transplant recipients. In the general population, those with a life expectancy of 5–10 years are typically excluded from the cancer screening guidelines. Mortality rates in renal transplant patients vary depending on age and comorbidities at time of transplantation, but it should be noted that mortality after diagnosis of malignancy is high in this population. In Australia and New Zealand, the 5-year survival rate for a transplant patient after malignancy diagnosis had been less than 10%.[27] Those with a malignancy history prior to transplant factor into the limitations as well. Depending on the type of malignancy, patients should be deemed cancer-free for 2–5 years prior to transplant consideration. However, with better survival outcomes after transplant compared to maintenance on replacement therapy (RRT), development of novel chemotherapeutic agents and more individualized immunosuppression, there has been discussion that the current recommendations may be too restrictive. Prospective data in the transplant population is needed to provide better guidance to the clinician regarding cancer screening.

MANAGEMENT

The cornerstone of post-transplant malignancy management is the reduction of immunosuppression. Management depends on the type and severity of malignancy and the benefits of decreasing immunosuppression to fight the cancer must be weighed against possible allograft rejection and/or failure. Targeting a lower immunosuppressant drug level is commonplace in the setting of malignancy, and clinicians may choose to transition from CNI to mTOR inhibitors (especially in the setting of skin cancers). There is some evidence to suggest mTOR inhibitors have anti-neoplastic properties and may be helpful in bridging the difficult gap between malignancy management and allograft protection, although this is not true of all cancers and more information is needed.

Another approach to the management of post-transplant malignancies is to withdraw entire classes of immunosuppression altogether. Although immunosuppression regimens are transplant center-dependent, the majority of programs are still using a three-drug regimen consisting of a CNI, anti-metabolite (mycophenolate mofetil or azathioprine), and prednisone.[2] In addition to changing the CNI to an mTOR inhibitor, the clinician may elect to discontinue the anti-metabolite medication to lower the overall immunosuppressive burden. This would seem more beneficial in those taking azathioprine, as it has been linked to neoplasia while mycophenolate mofetil may reduce the relative risk of some malignancies such as PTLD.[30]

Chemotherapy may be used depending on the type of

malignancy encountered. Perhaps the most challenging scenario is when faced with a malignancy which is typically responsive to immunotherapy. More recent breakthroughs in oncology have brought immunotherapy to the forefront of cancer treatment. Some of these therapies provide improved outcomes compared to the previous standard of care, and the immune checkpoint inhibitors have been the most successful types of immunotherapy to date. The clinical dilemma involves activation of T-cells to combat neoplastic cell growth. Activation of previously dormant T-cells (thanks to immunosuppression) can lead to allograft rejection due to recognition of donor antigen in the kidney.[31] An individualized approach to each transplant patient with malignancy is likely best to determine the best course of action.

SUMMARY

In the modern era of immunosuppression, we are seeing better outcomes in renal transplant recipients. As a result, the effects of prolonged exposure to immunosuppression, such as post-transplant malignancy, are more pronounced. A transplant recipient's previous medical and oncologic history, opportunistic viral exposures, and immunosuppression regimen should all be considered when managing or screening for post-transplant malignancy. Screening guidelines in transplant patients are often adopted from those of the general population, and more prospective evidence is needed for future guidance. Reduction in immunosuppression is a cornerstone of post-transplant malignancy management, and there is some evidence to suggest mTOR inhibitors and the anti-metabolite mycophenolate mofetil are less "oncogenic" compared to CNIs or azathioprine. Finally, all decisions to reduce immunosuppression and/or treat active malignancy must be weighed with the possibility of allograft rejection/failure and should be made in consultation with the patient's transplant team.

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Managing Side Effects of Immunosuppressants

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KEYWORDS: solid organ transplant, immunosuppression, side effects

INTRODUCTION

Maintaining an allograft after solid organ transplant (SOT) requires maintenance immunosuppression to prevent rejection and preserve organ function. While there have been improvements in the toxicities of maintenance regimens over the decades, transplant patients are still at high risk of developing side effects to their immunosuppression therapies. These can range from cosmetic changes, metabolic abnormalities, and toxicities to different organ systems.[1-3]

Medication adherence remains a significant challenge for SOT recipients. While difficult to capture the exact scope of its prevalence, it has been reported that medication nonadherence ranges from 22–68% in the SOT community. This is significant due to medication nonadherence being identified as an independent risk factor for poor outcomes after SOT.[4] While there can be many reasons why a patient is non-compliant with their medications, the World Health Organization identified side effects as a significant treatment-related factor for nonadherence.[5] SOT recipients may also seek out alternative therapies to self-treat their side effects, which can have an impact on immunosuppression therapy and organ function.[6,7] A combination of a calcineurin inhibitor (CNI), antimetabolite, and a corticosteroid remains a common maintenance regimen for SOT recipients.[8] While efficacious, these medications are associated with many side effects that can impact patients' quality of life.[1-3] While it may not always be clinically appropriate to change a transplant recipient's medication or reduce their dose, it is important to recognize and manage these side effects.

CALCINEURIN INHIBITORS

Cyclosporine was the first CNI used in SOT, which dramatically changed recipient outcomes.[2] Now, tacrolimus has become the CNI of choice due to its lower rejection rates and trends for increased patient survival.[9] Despite their benefits, CNIs are associated with numerous toxicities such as neurotoxicity, nephrotoxicity, development of new onset diabetes after transplant (NODAT), and cosmetic changes.[1,2,10] In recent years there has been an interest in investigating CNI withdrawal and avoidance regimens in order to avoid the toxicities associated with their long-term use.[2]

Tacrolimus is very lipophilic and plasma bound, which increases its ability to cross the blood-brain barrier. The presence of tacrolimus in the central nervous system may lead to the over production of endothelin, which, if introduced to vascular smooth muscle, can cause vasocontraction and vasospasm. The spectrum of tacrolimus neurological-related side effects includes, insomnia, headache, tremor, mood changes, and seizures.[10] To help prevent these side effects, therapeutic drug monitoring is used to make sure serum concentrations stay within therapeutic range. Analgesic medications can be used to relieve headache and sleep aids can be employed to help with insomnia. Conversion to an extended release tacrolimus product may help reduce certain peak-related side effects, such as tremors.[11] In cases of severe side effects like seizure, discontinuation of tacrolimus may be required. Alternative therapies may conclude conversion to cyclosporine, sirolimus, or belatacept.

The nephrotoxicity of CNIs remains a major concern in the transplant community. Afferent arteriolar vasoconstriction, activation of rein-angiotensin-aldosterone-system, and release of endothelin can lead to acute renal injury. Irreversible structural abnormalities in the kidney are seen after long-term use. Close therapeutic drug monitoring is utilized to prevent acute renal injury, by avoiding supratherapeutic serum concentrations. Use of dihydropyridine calcium channel blockers in patients with concomitant hypertension may counteract the vasoconstriction on the renal artery. There is no evidence to suggest that tacrolimus is less nephrotoxic than cyclosporine. CNI withdrawal and avoidance regimens have been studied with alterative immunosuppression therapies such as sirolimus, everolimus, or belatacept. While there may be long-term benefits of limiting CNI use in SOT recipients, these potential benefits must be balanced with the risks of rejection and graft loss.[2]

Tacrolimus can cause alopecia in 3–6% of patients.[12] Vitamin supplementation with biotin may be beneficial in protecting hair strength. If impacting the SOT recipient's quality of life, alternative immunosuppression therapies may be considered for certain patients. Conversion to cyclosporine can be considered, but hirsutism and gingival hyperplasia can occur.[1] Sirolimus or everolimus can be considered, but acne is a potential cosmetic side effect.

ANTIMETABOLITES

Mycophenolate is the most common antimetabolite currently used in SOT.[8] It has two different preparations; mycophenolate mofetil (MMF) and enteric-coated, mycophenolate sodium (EC-MPA). Both preparations are equally efficacious and have similar safety profiles.[13] Among transplant centers, there will be varying practices as to whether they prefer MMF or MPA for their SOT recipients. Azathioprine is an older antimetabolite that has been used for decades in SOT. Azathioprine's place in therapy is now usually reserved for patients who are unable to tolerate the mycophenolate products or trying to conceive.

Gastrointestinal (GI) side effects are common with mycophenolate products. Mycophenolate, after it is converted to mycophenolic acid, disrupts the production of GI epithelial cells through its anti-proliferative properties.[14] Symptoms may include diarrhea, nausea, vomiting, dyspepsia, and abdominal pain. Depending on the severity of the of the GI side effect and other infectious causes of diarrhea have been ruled out, it may be reasonable to monitor the patient before making any interventions. If symptoms persist or become more severe, dose adjustments may be necessary.[14,15] The GI side effects of mycophenolate are dose dependent. Total daily dose reductions may be appropriate for some patients. However, lowering doses of immunosuppressive agents can increase the risk of rejection and additional allograft monitoring should be performed. An alternative strategy to lowering the total daily dose of mycophenolate is to split the total daily dose over three or four doses instead of two.[15] A limitation of increasing the dosing interval is that it does make regimens more complicated for patients.

Bone marrow suppression is another potential side effect of mycophenolate.[16,17] It has been reported that neutropenia occurs in 5–38% in the kidney transplant population. The evolution of neutropenia for SOT recipients is multifactorial, but medications, infections, and malignancies must all be considered.[17] After neutropenia is identified and infections have been ruled out, all medications should be assessed for their potential to cause bone marrow suppression. For certain patients, it may be preferred to discontinue other bone marrow suppressing medications prior to adjusting their immunosuppression. If neutropenia persists, decreasing or discontinuing the mycophenolate product may be required. Based on the degree of neutropenia, granulocyte colony-stimulating factors may need to be used until the absolute neutrophil count recovers to an acceptable limit.

CORTICOSTEROIDS

Corticosteroids have been utilized in SOT for decades. However, their long-term use has been associated with a significant number of side effects including: osteoporosis, bone fractures, cardiovascular disease, psychiatric disturbances, and dermatological changes.[3,10] The toxicities associated with glucocorticoid steroids are related to the average dose and cumulative duration of use.[3,16] Steroid reduction and withdrawal may be safe for some SOT recipients, but there are certain patient populations that require life-long use. The Scientific Registry of Transplant Recipients (SRTR) annual report from 2018 showed that only 30% of kidney transplant recipients are steroid free.[8] With their use still prevalent, it is important that SOT recipients receive monitoring for corticosteroid-related side effects.

Corticosteroids alter bone metabolism by reducing bone formation and increasing resorption. These changes in bone metabolism lead to an increase risk of bone fractures.[3,16] Bone-protective therapies can be considered for high-risk patients when initiating corticosteroid therapy. High-risk individuals may include patients >65, those with past fractures, or those with a history of osteopenia. Calcium, vitamin D supplementation, and bisphosphonate therapy have all been used as bone protective regimens.[16] Monitoring of bone mineral density is recommended for high-risk populations, prior to steroid corticosteroid therapy and after 1 year of therapy if prednisone doses are expected to be ≥5 mg per day.[3]

Corticosteroids are associated with precipitating or exacerbating cardiovascular risks factors such as hypertension, hyperglycemia, hyperlipidemia, and obesity.[3] Patients on long-term corticosteroids should be monitored for these side effects and counseled on lifestyle modifications with diet and exercise as appropriate. Additional pharmacologic therapies may need to be initiated if these risk factors cannot be controlled despite diet and exercise.[1,3,16]

The neurologic side effects of corticosteroids can range from insomnia, irritability, mood changes, mania, and depression. The onset of these symptoms usually presents within the first couple of days to weeks of therapy. Management usually consists of lowering the dose of the corticosteroid. However, additional management may include sleep aids, antidepressants, or antipsychotics for certain patients.[10]

DIETARY AND HERBAL SUPPLEMENTS

The use of alternative medicine has increased in the United States, with 36% of Americans admitting to using herbs, non-herbal supplements, and vitamins. These products are not subjected to safety and efficacy testing by the FDA and their manufacturing practices are not regulated, which can lead to product inconsistencies.[6] Frequently, dietary and herbal supplements are started without consulting a health care provider. When reconciling medications with SOT recipients, it is important to screen for dietary and herbal supplement use. For SOT recipients, dietary and herbal supplements can be associated with drug interactions, immune stimulating effects, and direct organ toxicity.[6,7]

The drug interactions associated with these products can be clinically significant by affecting serum concentrations

of immunosuppressant medications. St. John's Wort is an inducer of CYP3A4, CYP2C9, and P-glycoprotein (P-gp). The use of St. John's Wort in combination with a CNI would lead to decreased serum concentrations of cyclosporine or tacrolimus. Ginkgo biloba and milk thistle are inhibitors of CYP3A4, CYP2C9, and P-gp. Turmeric is another inhibitor of CYP3A4. The use of these herbs in combination with a CNI would increase the serum concentrations of cyclosporine or tacrolimus.[18]

Some dietary and herbal supplements are marketed as immune stimulants. The concern with these products in the SOT population is that they can precipitate an immune response and interfere with immunosuppression therapy.[7,18] Echinacea, ginseng, astragalus, and vitamin C are examples of herbs and supplements that have immune stimulating effects and generally should be avoided in the SOT population. Vitamin C may also be used to promote wound healing; if its use is required, the risks vs. benefits should be discussed with the patient's transplant provider.

Dietary and herbal supplements can also have a direct effect on renal and hepatic function. Supplements such as chromium, creatine, L-Lysine, and willow bark can be directly nephrotoxic. High-dose vitamin C (>60 g/day), ephedra, and cranberry have been reported to cause nephrolithiasis. Case reports of supplement-induced rhabdomyolysis have been reported with use of wormwood oil, licorice, and creatine.[6] Herbal supplements that are known to be hepatotoxic include: kava kava, comfrey, DHEA, bee pollen, vitamin E, green tea, echinacea, turmeric, and valerian.[6,7,18]

CONCLUSION

In conclusion, SOT recipients are at high risk for developing side effects and toxicities to their maintenance immunosuppressants. It is important to recognize and manage these side effects as they can impact patients' quality of life, affect medication adherence, and cause damage to different organ systems. Patients should be monitored for potential side effects and interventions should be made when clinically appropriate. Patients may require adjunctive therapies to help manage these side effects or modifications to their immunosuppressive regimens may be necessary. SOT recipients should be screened for use of dietary and herbal supplements, due to their potential impact on organ function and drug interactions. If changing a SOT recipient immunosuppression regimen, the risk and benefits must be considered and additional graft monitoring is required.

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Transplantation of Hepatitis C-Infected Kidneys into Uninfected Recipients: A Review of the Literature

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KEYWORDS: hepatitis C, direct-acting antiviral therapy, sustained viral response, clinical trials

INTRODUCTION

There is a severe shortage of available deceased donor kidneys for transplantation. In 2018, kidney transplants totaled 22,393, of a national waiting list of 78,675. Only 58% of patients removed from the waitlist were done so for transplant; the remaining 42% were removed due to death or because they became too ill for transplant.[1] Annual waitlist mortality is 5–7% annually, and increases with age and comorbidities such as diabetes. As our population ages and the average age on the waitlist increases, this mismatch of kidney supply and demand continues to grow. One rising source of deceased donor kidneys is from donors with overdose- related death. The opioid crisis in the United States is associated with both increasing rates of hepatitis C as well as overdose-related deaths. Overdose-related death accounted for only 1.1% of all donors in 2000 but 13.4% in 2017, and tended to be younger, and more likely to be infected with hepatitis C virus (HCV).[2] A recent advisory from the Centers for Disease Control and Prevention Health Alert Network revealed an accelerated increase in opioid overdose deaths during the COVID-19 pandemic.[3]

In the United States, patients on dialysis have a mortality rate that exceeds 20% during the first year of dialysis and 50% after 5 years. The prevalence of chronic kidney disease has steadily risen from 2000-2018.[4] Following kidney transplantation, most patients receive a doubling in their life expectancy.[5] Given the rise in opioid-related deaths, the prevalence of hepatitis C and the shortage of kidneys in the donor pool, a critical assessment of the criteria for transplantation is necessary. In the last ten years, there have been a few noteworthy changes that affect our understanding of high-risk organs. First, the use of nucleic acid amplification testing to detect viral load, and second, the development of direct-acting antiviral medications targeted against hepatitis C.

NUCLEIC ACID AMPLIFICATION TESTING

In 2015, the US Organ Procurement and Transplant Network (OPTN) mandated routine qualitative HCV nucleic acid testing (NAT) in all organ donors.[6] Nucleic acid amplification testing can be used to reveal viremia in a serologically negative patient, and is routinely performed for HIV-1 and HCV in blood donors in the United States.[7] Standard serology testing for HCV becomes positive ~70 days following infection, ~40 days with enhanced serology testing, and in 3–5 days with nucleic acid testing. This testing has allowed the creation of a new category of HCV donors, based on combined Ab and NAT results.[6] Both HCV Ab+/NAT+ and HCV Ab-/NAT+ donors are considered HCV positive. Donors who are HCV Ab–/NAT– are usually deemed negative.

There are a few conditions in which a person may be HCV Ab+/NAT– including a false positive HCV antibody test, testing during the window period, donors with previous HCV infection who are in the process of clearing the virus while on therapy or have cleared the virus. The most common condition for HCV Ab+/NAT– appears to be prior HCV infection with spontaneous immunologic viral clearance.[8] The incidence of spontaneous immunologic clearance is estimated to be around 25% based on a 2006 systematic literature review.[9]

There is a window period which may occur if a donor dies of an intravenous drug overdose and the serologic testing is done a few days after the exposure, for example. In this case the Ab may be positive from prior exposure but NAT may not yet be positive from this exposure, leading to HCV Ab+/NAT–. Or if the donor was never previously exposed, they may be HCV Ab–/NAT–. Alternatively, if there was no prior exposure, and testing was after the 3-5 day period, the donor would be HCV Ab-/NAT+.

In a retrospective review published in the American Journal of Transplantation in 2019, short-term outcomes of adult deceased donor kidney transplants of HCV uninfected recipients were compared with either HCV Ab+/NAT- or HCV Ab+/NAT+. In this study, data was analyzed from the OPTN STAR files from the United Network of Organ Sharing (UNOS), which includes data submitted by members on all donors, waitlisted candidates and transplanted recipients. Patients were included from January 2015 to June 2018, were over the age of 18, and underwent deceased donor kidney transplantation (DDKT). Patients receiving simultaneous kidney-pancreas or other multiorgan transplants were excluded. The primary outcomes were length of stay, delayed graft function, rejection rate, serum creatinine at 6

months post transplant. Delayed graft function was defined as requiring dialysis in the first week post transplant. Secondary outcomes included overall graft and patient survival at 12 months. There were 42,240 DDKT recipients studied, with 33,934 DDKT from HCV-uninfected donors to HCV-uninfected recipients, 352 from HCV Ab+/NAT– donors to uninfected recipients and 196 HCV Ab+/NAT+ donors to uninfected recipients. There was no statistical difference in overall graft survival among the three groups. For HCV Ab+/NAT-, there was no difference in length of stay, rejection rate or serum creatinine. Finally, there was no statistically significant difference in overall graft survival at 12 months post transplant. For HCV Ab+/NAT+ donors to uninfected recipients, there was actually a lower proportion of delayed graft function and decreased serum creatinine at 6 months. There was no difference in graft survival. When compared to the reference group (HCV uninfected donors), uninfected recipients of HCV viremic donors had a shorter time on the transplant waitlist and dialysis and a lower KDPI (kidney donor profile index) score. Lower KDPI score reflects an overall better quality donor kidney. These findings are profoundly clinically relevant, in demonstrating non-inferior outcomes with HCV positive organs. A major limitation of the study was that the use of a direct acting antiviral was not included.[10]

Many single center studies have evaluated the rate of transmission of HCV from HCV Ab+/NAT– to an HCV Ab- recipient, with almost all studies reporting a zero rate of transmission. The largest of this type of study comes from the University of Cincinnati published in 2019, which analyzed the incidence of HCV transmissions and clinical outcomes in HCV-naive kidney transplant recipients who received allografts from HCV Ab+/NAT- donors. The primary outcome was incidence of HCV transmission at 3-months post transplant. For recipients who developed HCV viremia post-kidney transplant, direct-acting antiviral therapy was initiated. Secondary outcomes included post-kidney transplant graft function, graft survival, and patient survival at time of follow-up. During the study period of July 2016 to February 2018, 163 deceased donor kidney transplants occurred with 52 kidneys (32%) from HCV Ab+/NAT– donors to HCV negative recipients. There was a single potential transmission identified. In this one case, the donor was tested at day 2 and found to be NAT- and was transplanted. The recipient returned with HCV RNA positivity, so samples from the donor taken from hospital day 4 were sent for NAT and found to be positive. In this case, the donor likely became infected shortly before his death, which put him just before the capability for NAT detection, in the window period. This would indicate a 1.69% transmission incidence.[6]

Interestingly, national surveys conducted by Kucirka and colleagues found that providers were more likely to consider a high-risk organ if NAT was performed. When HCV NAT was performed, there was a 2.69 fold higher odds of utilizing high- risk donors. It could be concluded that performing this test may influence provider bias about high-risk organs.[11]

DIRECT-ACTING ANTIVIRAL THERAPY

The advent of HCV direct-acting antivirals (DAAs) has allowed for new protocols to be studied in HCV recipients. These allow for treatment of both patients with ESRD and those post transplant. There are currently several choices, and they are frequently used in combination. There are many trials using different agents, administered at different timing, and for varied duration of treatment. Detailed below are a few representative trials with very promising results.

Elbasvir/grazoprevir was studied in genotype 1 infected patients in the C-SURER trial and the pangenotypic combination of glecaprevir/pibrentasvir in the EXPEDITION 4 trial. Both demonstrated excellent safety and efficacy in those with ESRD, including those on dialysis. Elbasvir/grazoprevir for 12 weeks resulted in a sustained viral response of 99%, and a response of 100% seen with glecaprevir/pibrentasvir for 12 weeks.[8]

The THINKER clinical trial at the University of Pennsylvania demonstrated excellent allograft function and cure of HCV infection in 10 HCV negative patients who received kidney transplants infected with genotype 1 HCV. All recipients had detectable HCV RNA on post-operative day 3, had elbasvir/grazoprevir initiated, and by 12 weeks had sustained viral response.[12] Twelve-month follow-up of 20 such patients demonstrated HCV cure and comparable allograft function to matched HCV-negative recipient controls for all recipients.[13]

A clinical trial at Johns Hopkins University evaluated the transplantation of HCV+ donors into negative recipients in combination with direct-acting antivirals as both pre- and post-transplant prophylaxis. Each recipient received grazoprevir/elbasvir prior to transplantation and continued with daily therapy for 12 weeks. Three patients also took sofosbuvir due to their strain of HCV. In 7 out of 10 recipients, HCV RNA was undetectable at all times. No participant had virologic or clinical evidence of chronic HCV infection with a follow-up period of 12 weeks after the discontinuation of DAA and there were no adverse events related to treatment.[14]

Furthermore, there is an ongoing trial now evaluating the safety of HCV+ organ donation with DAA therapy with a shortened course. Thirty HCV negative patients were enrolled in the trial and received HCV Ab+/NAT+ lung, kidney, heart, or kidney-pancreas transplants. All recipients received a single dose of ezetimibe and glecaprevir/pibrentasvir before transplant and once a day for 7 days after surgery. While low-level viremia was transiently detected in 21 of 30 patients, all 30 transplant recipients had undetectable HCV RNA at 12 weeks post transplant.[15]

ADDITIONAL CONSIDERATIONS

The cost of treatment with DAA therapy versus waiting for a HCV Ab- donor was analyzed by Gupta and colleagues in 2018. The group compared renal transplantation from an HCV+ donor into an HCV recipient followed by immediate DAA therapy versus HCV recipients continuing dialysis and waiting for renal transplantation from an HCV donor, over a 5-year time frame. Estimates of cost were determined by Medicare reimbursements or kidney transplant Diagnosis-Related Groups and corresponding provider costs. Their model estimated that patients receiving HCV+ organs and undergoing DAA therapy resulted an estimated $190,000 less cost compared to continuing hemodialysis.[16]

The discussion of HCV+ kidney offers with potential transplant recipients continues to evolve. As we have more data about donor and recipient status, as well as growing prior experience, we can be more specific in approach and counseling. Transplantation of HCV+ into HCV- recipients is currently only performed under research protocols, and very clear informed consent is obtained for participation. As this practice may transition from clinical trials to standard clinical practice, this discussion will need to become part of the routine transplant consent process, as transplant outcomes using HCV+ kidneys in the current DAA era are comparable.

FURTHER DISCUSSION

Outcomes from hepatitis C antibody positive donors, either viremic or not, appear to be as good as hepatitis C negative organs in terms of length of stay, rate of rejection, serum creatinine and 12-month rates of graft survival. Additionally, the rate of transmission from a NAT-donor remains exceedingly low with a single case report of transmission. In patients that do seroconvert from hepatitis C negative to positive, there are multiple drug therapies that exist that create sustained virologic response and are well tolerated in this patient population.

With this promising data, many questions remain, including the timing of administration of direct-acting antiviral medications – pre-exposure, post-exposure, or even delayed. Additional factors, including insurance coverage of direct-acting antiviral therapy are an important consideration. Perhaps in the future, hepatitis C organ donation may become the accepted standard practice in renal transplantation and for other organs as well.

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