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Kidney Transplantation in the Elderly

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Summary

There is an increase in the older incident end-stage renal disease population that is associated with an increasing prevalence of end-stage renal disease in the United States. This trend is paralleled by an increasing rate of kidney transplantation in the elderly. Although patient survival is lower in older versus younger kidney recipients, the elderly benefit from a reduction in mortality rate and improved quality of life with transplantation compared with dialysis. Immunologic, physiologic, and psychosocial factors influence transplant outcomes and should be recognized in the care of the elderly transplant patient. In this review, we discuss transplantation in the elderly patient, particularly the topics of access to transplantation, patient and graft survival, the impact of donor quality on transplant outcomes, immunology and immunosuppression of aging, and ethical considerations in the development of an equitable organ allocation scheme.

Keywords

Elderly; kidney transplant; aging; patient survival; graft survival

It generally is accepted that patients who receive a successful kidney transplant gain a survival benefit compared with remaining on dialysis. Wolfe et al,¹ using data from the United States Renal Data System (USRDS) of more than 250,000 incident dialysis patients from 1991 to 1996, reported that the survival of patients receiving a deceased donor kidney transplant was longer than that of patients maintained on dialysis while awaiting transplantation. Although the survival advantage of transplantation was most pronounced in younger end-stage renal disease (ESRD) patients, patients of all ages gained additional years of life with transplant compared with dialysis.¹ Therefore, because of this mortality benefit, kidney transplantation is the treatment modality of choice for ESRD.

According to USRDS data, the prevalence of ESRD in the United States is increasing disproportionately to its incidence, likely because patients are living longer with ESRD (see the article by Eggers in this issue). USRDS data also indicate that the incident ESRD population is aging. In 1990, there were 21,479 incident ESRD patients aged 65 or older in the United States; this number steadily increased to 53,842 by 2006 (see the article by Eggers in this issue). There was a slower increase in kidney transplantation in patients older than age 65 during the same time period, such that by 2006, patients older than age 65 accounted for 13.3% of all kidney transplant recipients.² Nevertheless, only a limited number of elderly ESRD patients

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are considered for transplantation. Although reasons for this are unclear, it is possible that stringent selection criteria, a perception among health care providers of limited utility of kidney transplantation in the elderly, and decreased interest in kidney transplantation among older patients may be contributing factors. In 2006, less than 6% of ESRD patients older than age 65 were placed on the deceased-donor waiting list.² Access to transplantation, defined by registration for the deceased-donor waiting list or receiving a live-donor renal transplant, decreases with advancing age and is particularly low for elderly women. There is a 30% decrease in access to transplantation for each decade increase in age; when compared with comorbidity-matched male counterparts, access to transplantation was 29% lower for women aged 65 to 75 and 59% lower for women older than age 75.³

Several factors need to be considered when evaluating an elderly recipient for transplantation. In addition to recipient comorbidities, donor quality, immunosuppression, dialysis vintage, and the strength of social support networks affect the success of transplantation. Furthermore, the impact of transplantation on quality of life and mortality is not equivalent in the older versus the younger patient.^{1,4} Given the persistent shortage of donor organs and the advancing age of the ESRD population, the ethical balance of utility (allocation of organs to those who derive the greatest benefit) versus justice (equal access to transplantation for all age groups) is a significant dilemma in the development of equitable organ allocation schemes. In this review, we discuss factors central to transplantation of the elderly recipient, including patient and graft survival, the impact of donor quality on transplant outcomes, immunology, and immunosuppression of the aging patient, and ethical considerations in organ allocation.

Patient and Allograft Outcomes in the Elderly

Patient Survival

Numerous studies have indicated that there is less mortality in patients who receive a kidney transplant compared with those who remain on dialysis. Wolfe et al¹ compared mortality rates of deceased donor kidney transplant recipients with a comparable population of wait-listed dialysis patients. When the study was published in 1999, only about 1% of ESRD patients older than age 70 received a deceased donor renal transplant in the United States. Therefore, patients older than age 70 were excluded from the analysis. In an analysis of patient survival from the time of initial placement on the transplant waiting list, the relative risk of death 18 months after kidney transplant was lower in all age groups compared with the reference group of wait-listed dialysis patients.¹ However, when projected life years were compared between transplantation and dialysis, a greater mortality benefit was estimated for younger transplant recipients than older recipients (17 additional years of life with transplant for patients aged 20-39, and 11 years for patients aged 40-59 compared with 4 years for patients older than age 60).¹

Taking into account a recent increase in transplantation rates in older patients, a similarly designed study was conducted in 2007 by Rao et al⁵ using data reported by US transplant centers on patients older than age 70 to the Organ Procurement and Transplantation Network (OPTN)/Scientific Registry of Renal Transplant Recipients. Transplant recipients older than age 70 had a lower risk for mortality compared with wait-listed dialysis patients (age 70-74 y: RR, 0.59; 95% CI, 0.53-0.65; age ≥ 75 : RR, 0.58; 95% CI, 0.52-0.65).⁵ Furthermore, a survival benefit also was seen in elderly recipients of an expanded criteria donor (ECD) kidney (RR mortality of ECD versus wait-list: 0.75; 95% CI, 0.65-0.86),⁵ defined as one from a donor age 60 or older or a donor aged 50 to 59 with two of the following: hypertension, death from stroke, or terminal creatinine level greater than 1.5.^{5,6}

A smaller study by Oniscu et al⁷ compared mortality between renal transplant recipients and wait-listed dialysis patients older than the age of 60 in Scotland. Although there was a higher risk of death in the first 30 days compared with dialysis (RR, 4.91; 95% CI, 2.09-11.52),

transplantation was associated with a lower risk of death thereafter (31-365 days posttransplant: RR, 0.71; 95% CI, 0.35-1.41; and >365 days posttransplant: RR, 0.35; 95% CI, 0.22-0.54).⁷ The estimated life expectancy was approximately 4 years greater with a kidney transplant than remaining on dialysis.⁷ Furthermore, an Australian study also reported a survival benefit in renal transplant recipients older than the age of 60 compared with dialysis.⁸

Relative Benefit of Transplantation: Older Versus Younger Recipients

Even though there is evidence of a survival benefit for the elderly who receive a kidney transplant compared with staying on dialysis, numerous studies have suggested that the survival benefit is less for the elderly compared with younger transplant recipients,^{1,4,9-13} and a decrease in allograft survival among elderly transplant recipients has been reported consistently.¹⁴⁻¹⁶ Taking into account an expected increased mortality in the elderly population, both graft survival and death-censored graft survival (ie, graft survival excluding death with a functioning graft) are equally important measures of allograft outcome in elderly transplant recipients. Meier-Kriesche et al,¹⁵ using kidney transplant data submitted to the United States Renal Transplant Scientific Registry between 1988 and 1997, reported that both graft survival and death-censored graft survival were significantly lower in kidney transplant recipients older than age 65 compared with younger age groups. However, a later study using OPTN data incorporated a longer period of follow-up evaluation on kidney recipients from a later era (1995-2000) and found that although graft survival worsened as recipient age increased, death-censored graft survival improved with advancing age.¹⁶ Analogous data from other studies examining graft outcomes in transplant recipients from more recent years support that there is little difference in death-censored graft survival in older recipients compared with younger recipients.^{14,17-19}

The causes of graft loss differ depending on the age of the recipient. Observational studies have noted a decreasing rate of acute rejection with advancing age.^{17,20} Nevertheless, the impact of acute rejection on graft loss may be more pronounced in the elderly. Meier-Kriesche et al²¹ reported that the 5-year death-censored graft survival adjusted for donor and recipient characteristics in patients who experienced an episode of acute rejection within the first 6 transplant months was 82.1% in patients aged 18 to 35 compared with 59.9% in patients older than age 65. Although graft loss owing to an immunologic cause is more common in the younger transplant population, death with a functioning graft is the most common cause of graft loss in the elderly.^{14,22} Compared with transplant recipients between the ages of 18 to 29, patients older than age 65 are seven times more likely to die with a functioning graft.²³

Effect of Donor Characteristics on Transplant Outcomes

Because elderly recipients are more likely to die with a functioning graft, some have argued that older or marginal kidneys should be allocated preferentially to older recipients. In the United States, the United Network for Organ Sharing allocation scheme does not take into account age-matching of donor and recipient and the decision to waitlist a patient for an ECD kidney is left to the discretion of the transplant center. In 2006, 34.3% of ECD kidneys were given to patients older than age 65 in the United States.²⁴ However, to what extent does donor quality affect graft survival and/or mortality in the elderly population?

Effect of Waiting Time

ECD kidneys may be an attractive option for elderly transplant candidates because they can reduce the waiting period for a transplant. The detrimental effect of prolonged waiting time on allograft outcomes was illustrated in a comparative analysis of kidney transplant survival with paired donor kidneys given to patients on dialysis for longer than 2 years compared with those on dialysis for less than 6 months.²⁵ Patients who received dialysis for a longer duration of

time before the transplant had lower 5- and 10-year graft survival rates.²⁵ Additional studies have indicated that the survival benefit with transplantation is greatest in recipients who have the shortest waiting time.^{26,27} However, by definition, ECD kidneys are associated with a higher risk of graft loss compared with standard criteria donor (SCD) kidneys. Allograft and patient survival for individuals older than age 60 are worse for recipients of ECD kidneys compared with those of living donor and SCD kidneys, even after adjusting for duration of pretransplant dialysis and other donor and recipient factors.²² Furthermore, individuals older than age 60 who received an ECD kidney had worse renal function at 1 year compared with recipients of a living donor or SCD kidney.²²

The European Experience

Eurotransplant Seniors Program initiative—In an initiative to reduce waiting time for elderly recipients, the Eurotransplant Seniors Program (ESP) was developed to match the life expectancy of organs and recipients by allocating older deceased donor kidneys to elderly recipients. ESP became fully implemented into the Eurotransplant Kidney Allocation System in January 2001. The ESP algorithm allocates kidneys from donors older than age 65 to recipients older than age 65 within a local or narrow geographic area to minimize cold ischemia time. Organs are allocated by blood group and waiting time only. Candidates older than age 65 may be eligible to receive organs from donors younger than age 65 if they do not consent for ESP. These younger organs continue to be allocated under the Eurotransplant Kidney Allocation System, which allocates according to the degree of HLA mismatch, waiting time, expected cold ischemia time, and the balance of donors and recipients between countries in the Eurotransplant region.

ESP outcomes—The 5-year outcomes of recipients transplanted under ESP were reported recently in 2008.¹² In the ESP era, the median waiting time increased for younger recipients, perhaps because of an increasing number of patients on the transplant waiting list, whereas waiting time decreased for recipients older than age 65.¹² However, 5-year patient and graft survival rates were worse for those older than age 65 who received an older kidney under ESP (60% and 47%, respectively) compared with those for recipients aged 60 to 64 who received a kidney under the Eurotransplant Kidney Allocation System (74% and 64%, respectively).¹² Thus, the ESP experience indicates that elderly transplant patients fare better by receiving a transplant from a younger donor. However, the mortality rate of patients transplanted under ESP has not been compared with that of wait-listed dialysis patients, and therefore the relative benefit of earlier transplantation under the ESP algorithm compared with waiting for a younger deceased donor kidney is not known.

Effect of ECD Transplantation on Life Expectancy

It is important to characterize which patients would benefit from accepting a marginal kidney in exchange for earlier transplantation. To address this question, Schold and Meier-Kriesche²⁸ used data from the Scientific Registry of Renal Transplant Recipients database to project life expectancy for wait-listed candidates and living donor, SCD, and ECD transplant recipients in the United States. The life expectancy for ECD recipients older than age 65 who received earlier transplantation (defined as <2 years of dialysis; 5.6 y; 95% CI, 5.1-6.5) was similar to that for later transplantation (>4 years of dialysis) with a living donor (5.5 y; 95% CI, 4.7-6.5) or SCD kidney (5.3 y; 95% CI, 4.8-6.0).²⁸ Patients with a primary diagnosis of diabetes in all age groups had a similar life expectancy with earlier ECD transplantation compared with later SCD transplantation.²⁸ It is important to note that perioperative factors including the risks of the surgical procedure, anesthesia, delayed graft function, and heightened immunosuppression contribute to an increased risk for mortality early after transplantation compared with dialysis. However, the long-term risk (>226 days posttransplant) for mortality with transplant is lower than that of dialysis.²⁷ In regions of the United States with long median

waiting times (>1,350 days), subgroups associated with a survival benefit from ECD transplantation include recipients older than age 40, both sexes, all races, non-Hispanic ethnicity, unsensitized patients, and diabetes and hypertension as a cause of ESRD.²⁷ In contrast, in regions with a shorter median waiting time (<1,350 days), only recipients with diabetes as a cause of ESRD had a survival benefit with ECD transplantation.²⁷

Summary and Conclusions

It can be inferred from these data that ECD transplantation should be offered to all elderly candidates without a living donor who otherwise would have a prolonged wait for a SCD kidney and all elderly diabetic candidates regardless of anticipated waiting time. In contrast, we have found in our clinical experience that elderly patients who receive a kidney that does not work well frequently have increased morbidity and mortality than younger recipients of poorly functioning grafts.

Influence of Recipient Age on Mortality

Effect of Comorbid Conditions

Elderly recipients are more likely to have comorbid conditions at the time of transplant than younger patients. These conditions are associated with higher posttransplant mortality. An observational study of the OPTN/United Network for Organ Sharing database examined the influence of recipient comorbidities, including a history of angina/coronary artery disease, peripheral vascular disease, cerebrovascular disease, malignancy, chronic obstructive pulmonary disease, and diabetes on short-term mortality (within 90 and 365 days after transplant) in older patients.²⁹ Older patients were more likely to have comorbid conditions at the time of transplant than their younger counterparts (48.2% of recipients older than age 60 had no comorbidities compared with 28.9% of patients younger than age 60).²⁹ In patients older than age 60, a history of angina/coronary artery disease, chronic obstructive pulmonary disease, or diabetes increased the odds of 1-year mortality anywhere from 30% to 121% compared with recipients older than age 60 with no comorbidities.²⁹ When patients older than age 60 received an ECD kidney or experienced delayed graft function, the presence of any of the earlier-described 6 comorbidities increased the odds of mortality in the first year on the order of 59% to 351%.²⁹

Cardiovascular Disease

The risk of cardiovascular disease increases with the progression of kidney disease³⁰ and cardiovascular disease accounts for 38% of all deaths in the ESRD population.² Side effects of commonly used immunosuppressive medications include weight gain, diabetes, hypercholesterolemia, and hypertension, all of which may contribute significantly to cardiovascular risk. Similar to the dialysis population, the most common cause of death in kidney transplant patients is cardiovascular disease.²³ Although there is a linear increase in cardiovascular mortality with age in both wait-listed patients awaiting a transplant and transplant recipients, the rate of increase in cardiovascular mortality with age in wait-listed patients exceeds that of transplant recipients (Fig. 1A).³¹ Furthermore, the risk of cardiovascular death for all age groups is greater for wait-listed patients than for transplant patients (Fig. 1A).³¹ Thus, it can be inferred that transplantation is associated with a decreased risk of cardiovascular death compared with dialysis. In addition, although advancing age increases the risk for cardiovascular death in ESRD patients, transplantation attenuates the effect of age on cardiovascular mortality.

Infectious Disease

Infection-related mortality is the second most common cause of death in the ESRD and transplant populations.² In general, older patients are more susceptible to infectious death than younger patients,²⁰ however, age has a greater impact on infection-related mortality in transplant patients compared with its effect in their dialysis counterparts. In a study of cause-specific mortality rates in the ESRD population, transplanted patients had an exponential increase in the risk of infectious death by age, whereas only a linear association between infectious death and age was observed in wait-listed patients (Fig. 1B).³¹ Another study reported that infectious death represents the most common cause of first-year mortality in transplant patients older than age 60, a period during which the relative degree of immunosuppression is the highest (Fig. 2).²⁹ These data show that the elderly are more vulnerable to the effects of immunosuppression, perhaps because of age-related immunosenescence. Nevertheless, despite the increased effect of age on infectious death with transplantation, transplantation is associated with a lower risk of infection-related mortality in all age groups compared with dialysis.³¹

Summary and Conclusions

Thus, although older transplant patients have a higher risk for mortality than their younger counterparts, elderly transplant patients have a lower risk of all-cause mortality and death caused by cardiovascular disease and infections than dialysis.

The Immunology of Aging

Introduction

It generally is assumed that aging is associated with a progressive decline in immune function. However, the aging phenotype is heterogeneous and immune constitution is variable in healthy older adults compared with elderly transplant recipients with comorbidities. Some of the changes in immunity occur in all adults as a natural byproduct of aging; others are greatly affected by co-existing illness. As a consequence, some elderly transplant recipients may be more susceptible to overimmunosuppression whereas others may have a greater tendency to reject.

Table 1 summarizes the changes that occur with immunosenescence. The immune system consists of innate immunity, comprised mainly of monocytes, natural killer cells, and dendritic cells, and adaptive immunity, involving T and B lymphocytes. Immunosenescence affects both branches; however, aging has a greater effect on adaptive immunity. These changes result in part from thymic involution, replicative senescence, and atrophy of secondary lymphoid organs, leading to a decrement in circulating lymphocytes and altered cytokine profiles.

Hematopoiesis and Stem Cells

There is evidence that hematopoiesis is impaired with aging. The stem cell compartment is believed to consist of distinct categories of lineage-biased hematopoietic stem cells (HSCs).³² These categories consist of lymphoid-biased HSCs, which primarily differentiate into lymphoid cells, myeloid-biased HSCs, which preferentially differentiate into myeloid cells, and balanced HSCs, which give rise to about 10% myeloid and 90% lymphoid cells.³³ Myeloid-based HSCs have a blunted response to the lymphopoietin, interleukin-7, resulting in a limited capacity to generate T- and B-lymphocyte precursors.³⁴ Furthermore, myeloid-based donor HSCs are slow to repopulate after transplantation into irradiated mice³⁴ whereas lymphoid-biased HSCs respond more quickly to hematopoietic stress.³³ Clonal studies in a murine model suggest that a shift in the stem cell compartment from predominantly lymphoid-biased to myeloid-biased HSCs occurs with aging,³⁵ and this may help to explain the attenuated hematopoietic response of the aged individual.

Adaptive Immunity

The critical steps of thymocyte development occur in the thymus, including somatic rearrangement of the T-cell receptor (TCR) genes, which accounts for the diversity of TCR specificities on naive T cells. A broad repertoire of TCR specificities is crucial for immune activation to a diverse set of foreign antigens. Thymic involution begins during puberty and progresses at a rate of about 3% per year until middle age, whereupon the rate of atrophy decreases to about 1% per year.³⁶ This process leads to a reduction in thymic output of naive T lymphocytes,³⁷ down-regulation of TCR gene rearrangement,³⁸ and a greater reliance on peripheral memory cells and terminally differentiated effector T cells.³⁹ As a consequence, the range of TCR diversity becomes progressively more limited with aging.

Thymic output also is important for immune reconstitution after cytoreductive therapy. This has been shown in several studies examining the rate of T-lymphocyte repopulation after myeloablative chemotherapy.^{40,41} TCR rearrangement excision circles are episomal DNA circles generated during arrangement of TCR genes and are a useful marker of thymic output.^{42,43} In a study of 40 adults aged 34 to 66 years who received myeloablative chemotherapy followed by autologous stem cell transplantation for multiple myeloma, there was a negative correlation between age and T-lymphocyte reconstitution as measured by numbers of TCR rearrangement excision circles at 6 months and 1 year after engraftment.⁴¹

Cellular immunity may be impaired during the aging process through the action of regulatory T cells (T_{reg}). T_{reg} cells have been shown to suppress the activation, proliferation, and cytokine production of effector T cells^{44,45} and their absence has been associated with the development of autoimmunity.⁴⁶ Studies of healthy volunteers have reported that T_{reg} cells accumulate with aging.^{47,48} Furthermore, elderly individuals with comorbid conditions have higher levels of peripheral blood T_{reg} cells than their healthy counterparts,⁴⁸ suggesting that the action of T_{reg} cells may lead to an enhanced susceptibility to infectious illness in the nonhealthy elderly population. The role of T_{reg} cells in kidney transplantation remains unclear, with conflicting evidence regarding their impact on acute rejection.⁴⁹⁻⁵² However, it is tempting to postulate that T_{reg} cells participate in the increased vulnerability of the elderly transplant recipient to the effects of immunosuppression.

Summary and Conclusions

Changes in both innate and adaptive immunity occur with aging, which may help to explain an increased susceptibility to infectious illness and the decreased acute rejection observed in elderly transplant recipients.²⁰

Immunosuppression in the Elderly Transplant Recipient

Introduction

Few studies have carefully evaluated the impact of different immunosuppressive drug protocols in the elderly. Many of the earlier prospective clinical trials did not include a significant number of elderly transplant recipients and much of the evidence concerning the effect of specific immunosuppressive agents arises from retrospective database studies or small observational series. Given the paucity of data, it is difficult to draw conclusions on the pharmacodynamic effects of specific immunosuppressive agents in the elderly.

Pharmacokinetics

Physiologic changes that occur in aging may alter drug pharmacokinetics. Bioavailability may be influenced by decreased intestinal or hepatic first-pass metabolism⁵³ and the volume of distribution of lipophilic drugs, such as cyclosporine, may increase as the relative fat content increases with age.⁵⁴ Protein binding may decrease by up to 15% to 25% in elderly individuals

compared with younger adults, which can lead to increased free plasma concentrations of immunosuppressive medications.⁵⁵ This is particularly relevant in the case of mycophenolic acid, in which the free fraction represents the active inhibitory component to inosine monophosphate dehydrogenase.⁵⁶ Hypoalbuminemia may result in increased exposure to mycophenolic acid, thereby enhancing the immunosuppressive effect of mycophenolic acid and increasing the risk for drug toxicity.⁵⁶ Furthermore, aging is associated with reduced hepatic and renal clearance, which may be compounded by cofactors such as frailty, comorbidity, and polypharmacy.⁵⁷

In a study of cyclosporine pharmacokinetics, elderly transplant recipients (defined as >65 y) required significantly lower doses of cyclosporine to achieve similar target drug concentrations as young recipients.⁵⁸ In addition, clearance of cyclosporine was lower and intracellular T-lymphocyte concentrations of cyclosporine, which have been shown to negatively correlate with rejection,⁵⁹ were higher in elderly patients compared with younger patients.⁵⁸ Although pharmacodynamic data are lacking, these findings suggest that the elderly may have an increased susceptibility to the immunosuppressive effects of cyclosporine.

Immunosuppression and Infections

There are conflicting data on the effect of mycophenolate mofetil (MMF) on infectious outcomes in elderly renal transplant recipients. A small, single-center, observational study reported that patients older than age 60 receiving a maintenance regimen of cyclosporine, MMF, and prednisone had an increase in overall infections, opportunistic infections (mainly cytomegalovirus and fungal infections), and hospitalizations compared with similarly aged recipients receiving cyclosporine, azathioprine, and prednisone.⁶⁰ However, limitations of this study included a small sample size, differences in length of follow-up evaluation between each study group, different formulations of cyclosporine used (Sandimmune in the azathioprine arm, and Neoral in the MMF arm; both from Novartis Pharmaceuticals, Basel, Switzerland), and the inclusion of several tacrolimus-treated patients instead of cyclosporine in the MMF group. A later single-center retrospective study also suggested that MMF use was associated with a higher incidence of opportunistic infections (viral, fungal, and mycobacterial) and lower actuarial patient survival compared with azathioprine, but this study had similar limitations as the earlier-described study.⁶¹ In contrast, Sureshkumar and Nghiem⁶² reported greater patient and graft survival rates in MMF-treated elderly patients compared with azathioprine.

Summary and Conclusions

In light of the pharmacokinetic changes that may influence immunosuppression in the elderly, pharmacodynamic studies are needed to fully evaluate for differences in immunosuppressive potency that may exist in the older population. A variety of cofactors, including comorbidities, drug–drug interactions, diet, renal and hepatic function, and immunosenescence may influence the overall effect of immunosuppressive medications. These factors confound our ability to make generalizations about the effect of individual immunosuppressive drugs or drug protocols in the elderly and there is a need for refinement of immune monitoring assays to guide the choice and dosing of immunosuppression in older transplant recipients.

Ethical Considerations in Organ Allocation

Introduction

Given the persistent shortage of donor organs in the face of a steadily growing ESRD population, the earlier discussion highlights important ethical issues concerning allocation of scarce resources to the elderly. The evidence we have summarized leads one to conclude the following: (1) the survival benefit of transplantation over dialysis extends to the elderly population; (2) despite an increase in mortality, death-censored graft survival is comparable

for elderly transplant recipients compared with their younger counterparts; and (3) there is survival benefit associated with ECD transplantation compared with dialysis, however, patient and graft outcomes are worse with ECD transplantation compared with living donor and SCD transplantation. Both the elderly and younger transplant candidates may enjoy similar relative benefits with transplantation; however, younger patients generally have a greater life expectancy. Several ethical questions should be considered in light of the available data. Should younger patients have priority in receiving a younger deceased donor kidney, as is currently the policy in the United States? (Kidneys from donors younger than age 35 are offered preferentially, with some exceptions, to pediatric candidates.) Should older kidneys be restricted to the elderly population? Can living donor transplantation be justified when there is a limited benefit of additional life-years? A major consideration in the development of an equitable organ allocation scheme is the balance of utility, in which kidneys are offered to those candidates who would derive the greatest benefit from transplantation, versus justice, in which all age groups have equal access to deceased donor kidneys.

Organ Allocation

The ESP experience has shown that preferentially allocating older kidneys to older recipients can reduce waiting time for transplantation.¹² However, recipients older than age 65 who received older kidneys had lower patient and graft survival rates than recipients of younger deceased donor kidneys.¹² It is not known to what extent shorter waiting time has impacted outcomes in the elderly ESRD population in the Eurotransplant region. It would seem that a better measure of the ESP's success would be a comparison of outcomes of patients transplanted under ESP with a similar age-matched cohort on the transplant waiting list. Although these data are not available from Eurotransplant, data from the United States do indicate that transplantation of an elderly recipient with an older (ECD) kidney offers a survival benefit over dialysis.^{5,27,28}

In 2004, the OPTN/United Network for Organ Sharing Kidney Transplantation Committee sought to refine the deceased donor kidney allocation algorithm in an effort to create a more equitable allocation process. Their efforts culminated in a public forum held in Dallas, Texas, on February 8, 2007, that solicited recommendations on how to improve the current kidney allocation scheme. A major initiative arising out of the meeting was to develop an allocation scheme that would match anticipated survival of both the kidney allograft and the recipient by incorporating a measure of utility (estimate of life-years after transplant) and justice (time spent on dialysis) in relation to an estimate of donor quality (donor profile index). The committee currently is reviewing methods for estimating life-years after transplant,⁶³ and current iterations of these models were discussed at a second public forum in St. Louis, Missouri, on January 26, 2009. More information about the concepts under consideration for kidney allocation can be found at www.optn.org/kars.asp.

Quality of Life

The impact of transplantation on quality of life should be considered in a discussion of organ allocation and the elderly. In general, transplant patients report an improved quality of life compared with dialysis patients in measures of health perception, physical and social functioning, and vitality.⁶⁴⁻⁶⁶ The nationally standardized SF-36 (36-item short form) is a quality-of-life questionnaire encompassing 8 scales: physical functioning, role limitation due to physical health problems, bodily pain, social functioning, mental health, role limitation due to emotional problems, overall vitality (energy and fatigue), and general health perception.⁶⁷ Studies of older transplant recipients compared with similar-aged dialysis patients indicate that transplantation is associated with higher SF-36 scores.^{68,69} Among the predictors of improved health-related quality of life in the elderly transplant recipient are a lower rate of pretransplantation and posttransplant hospitalizations and fewer side effects of

immunosuppression,⁷⁰ reinforcing that a complicated posttransplant course may have a detrimental effect on perceived health status. Therefore, although elderly transplant candidates generally can anticipate an improved quality of life with transplantation over dialysis, identification of risk factors for posttransplant complications is paramount. Factors impacting transplant outcome that are prevalent in the elderly population include malnutrition, depression, poor functional status, and social isolation.⁷¹⁻⁷⁴

Summary and Conclusions

The decision to proceed with transplantation in the elderly candidate requires careful consideration of the individual-level risks weighted against the expected gains in life duration and quality.

Conclusions

In general, elderly ESRD patients benefit from kidney transplantation by gaining an increase in life expectancy and improved quality of life over dialysis. However, donor organs are a limited resource and equitable allocation of kidney transplants requires a balance between utility and justice. Similar to younger recipients, donor quality strongly impacts patient and transplant outcomes in the elderly, but allocation of older kidneys to older recipients may improve survival by decreasing transplant waiting time. It is important to recognize that risk factors such as malnutrition, depression, poor functional status, and social isolation may predict a complicated posttransplant course. As of yet, the upper age limit for transplantation has not been defined, although it seems that physiologic age, rather than chronologic age, would likely be a better predictor of posttransplant outcome. Advanced chronologic age, in and of itself, should not preclude a patient from kidney transplant because the available evidence suggests favorable transplant outcomes in the elderly. Therefore, after carefully weighing the risks and benefits of transplantation, elderly ESRD patients should continue to be considered for kidney transplantation, with case-by-case individualization rather than generalizations about therapeutic options based on age alone.

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Figure 1.

Incidence and prevalence rates of ESRD in the United States from 1980 to 2006. Adapted from the US Renal Data System, USRDS 2008 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2008. The data reported here have been supplied by the USRDS. The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the US government.

Figure 2.

Incident ESRD and kidney transplant counts in patients older than age 65 from 1990 to 2006 in the United States. Adapted from the US Renal Data System, USRDS 2008 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2008. The data reported here have been supplied by the USRDS. The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the US government.

Figure 3. The association of age on (A) cardiovascular and (B) infection-related mortality in wait-listed (gray bars) and transplant patients (black bars). Reprinted with permission from Meier-Kriesche et al.³¹

Figure 4. Causes of first-year mortality among renal transplant recipients older than age 60 in the United States. Adapted from Kauffman et al.²⁹

Table 1**Changes in Immunity in the Elderly**

Observation	Effect	References
Decreased stem cell production	Decreased hematopoiesis	75
Accumulation of myeloid-biased hematopoietic stem cells	Decreased lymphopoiesis	33-35
Attenuated development of thymocyte and B-cell progenitors	Decreased lymphopoiesis	76-78
Thymic involution	Reduction in naive T cells, limited TCR diversity	40,41,79,80
	Delayed immune reconstitution after cytoreductive therapy	
Reduction in peripheral dendritic cell population	Impaired T-cell proliferation and cytokine production	81
Altered cytokine profile	Increased IFN- γ , IL-6, IL-10, IL-12 Decreased IL-2 production	82-84,85
Increase in FOXP3 T _{reg} cells	Decreased effector T-cell and natural killer cell response	47,48,86
Decreased perforin expression	Deficient cytolytic activity	87

Abbreviations: IFN, interferon; IL, interleukin.