Oncologic Issues and Kidney Transplantation: A Review of Frequency, Mortality, and Screening

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Kidney transplant recipients are at increased risk for development of malignancy compared with the general population, and malignancies occur at an earlier age. This increased risk, as expressed by the standard incidence ratio (SIR), varies widely, but it is highest in malignancies triggered by oncogenic viruses. For other cancers, this increased risk is the direct consequence of immunosuppressants promoting tumor growth and lowering immune system tumor surveillance. In this review, we briefly discuss the common malignancies with increased risk after kidney transplantation, explore the pros and cons associated with screening, and summarize current prevention and treatment recommendations.

Key Words: Kidney transplant, Malignancy, Immunosuppression, Cancer screening

Introduction

Oncologic issues are important in patients with ESRD before and after kidney transplant. In the following review, we will review the incidence of cancer in kidney transplant recipients (KTRs), mechanisms for their increased incidence, and the effect on mortality. We will also briefly describe the malignancies that are most uniquely common to KTRs and review guidelines for prevention and screening. We will end with a discussion of when changes in immunosuppression should be considered based on the frequency of the cancer and the putative role of immunosuppression in its occurrence.

Pretransplant Issues

First, a word about cancer in patients with ESRD and its effect on their being listed for kidney transplant. In previous years, such patients would be denied listing until an appropriate cancer-free interval had elapsed. However, in more recent years, United Network for Organ Sharing (UNOS) regulations allow patients to be listed but made temporarily unavailable, which enables them to accrue time as they wait. Guidelines for suggested disease-free waiting periods for various cancers were published several years ago,[1] and to our knowledge they have not been updated. Details such as tumor size and pathologic description clearly affect this decision.

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Post-transplant Incidence and Causes

The overall risk of cancer post-transplant is considerably higher than in the general population,[2] and it is higher than in dialysis patients.[3,4] In more recent publications on this topic, the higher frequency of cancer in KTRs has been expressed as a standard incidence ratio (SIR), which is the incidence in KTRs compared with age-matched controls.[3,5] In Table 1, we have compiled a list of the SIRs for common cancers in the post-transplant population on the basis of data from several references.[2,3,6-13] Not only is the overall risk of cancer higher in KTRs, but it also occurs at an earlier age. For example, female KTRs 25 to 30 years old have a similar risk for cancer as do women 55 to 60 years old.[14] Similar occurrence of cancer at a younger age exists for male KTRs.[14] Although cancer risk is still elevated in older KTRs, it is not as dramatic as in younger patients (Fig 1). Accordingly, our efforts should target this higher risk (and by extension, more likely to derive benefit), younger group of patients.

Not all cancers occur at an increased frequency post-transplant. As depicted in Table 1, nonmelanoma skin cancer (NMSC) predominates as the most frequent cancer post-transplant, followed by post-transplant lymphoproliferative disorder (PTLD) and genitourinary and gynecologic cancers (cervix and vulva). Colon cancer occurs approximately 2 times more commonly. It is worth emphasizing that several common cancers, most notably breast and prostate, do not occur at an increased frequency and thus do not call for special consideration with regards to screening or changes in immunosuppression.

Reasons for the increased incidence of malignancy post-transplant relate to the direct effects of immunosuppressants as well as their effects to suppress immune surveillance and to stimulate the activation of oncogenic viruses.[7,15] Calcineurin inhibitors, such as cyclosporine and tacrolimus, have been demonstrated to stimulate transforming growth factor-β, interleukin-6, and vascular endothelial growth factor to promote

tumor growth in animal models.[16] Azathioprine sensitizes DNA to ultraviolet A radiation and cyclosporine inhibits DNA repair in ultraviolet-B-damaged keratinocytes, thus explaining the higher frequency of skin cancer with these agents.[17-19] Immunosuppression can also activate oncogenic viruses, which can immortalize infected cells by disrupting cell-cycle control, which then can lead, in a setting of induced lowered immune surveillance, to tumorigenesis. Such is thought to be the mechanism of the increased frequency of PTLD associated with activation of Epstein-Barr virus (EBV), Kaposi's sarcoma (associated with human herpes virus 8), cervical and vulvar cancer associated with human papilloma virus (HPV), and hepatocellular carcinoma associated with hepatitis C virus and hepatitis B virus (Table 2).[20]

Although death from cancer is a major contributor to mortality in KTRs, recent data challenge the notion that this is true across all age ranges. Examining death rates from cancer as reported in U.S. Renal Data Service data from 1990 to 2004, an increased mortality from cancer in younger patients (standardized cancer mortality ratio [SCMR] $>$ 1) was found; however, the death rate was lower from cancer in older patients (SCMR $<$ 1), especially those with diabetes.[21] The authors attribute these results to competing risks of death from other causes in older KTRs, a finding that has implications for screening, depending on age group. When comparing death from cancer across all age groups, the overall SCMR was 0.96 (95% confidence interval 0.92-1.00).[21]

CLINICAL SUMMARY

- Malignancy occurs with an increased frequency and at an earlier age in kidney transplant recipients (expressed as the standard incidence ratio [SIR]).
- The magnitude of this increased risk varies for each type of malignancy, but it appears to be greatest for those associated with an oncogenic virus.
- Post-transplant screening guidelines largely follow those established for the general population, although in patients with reduced survival (older and diabetic kidney recipients), screening may not be appropriate.
- Consideration for reduction in immunosuppression in kidney transplant recipients with advanced cancer may be most appropriate in cancers where the SIR is 3 or greater.

Description of Common Cancers Post-transplant

Certain post-transplant malignancies deserve special mention because of their increased frequency and high SIR. Guidelines for detection and screening have been described in Chapters 18-20 on malignancy in the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for the care of the kidney transplant patient[8] and commentary on these guidelines.[22]

Skin Cancer

NMSC is the most common post-transplant malignancy. Risks include fair skin phenotype, geographic location close to the equator, and time post-transplant.[23] The reported SIR of NMSC after kidney transplantation varies, but it is accepted to be high, ranging from 33 to 100.[9,10] Although the incidence of basal cell carcinoma exceeds that of squamous cell carcinoma 4:1 in the general population, the SIR for squamous cell carcinoma greatly exceeds that of basal cell carcinoma, making it more common after transplantation (ie, the ratio reverses).[10] Coupled with the high incidence of NMSC in the general population, it is not surprising that studies estimate approximately one third of all KTRs will have an episode of NMSC within 10 years after transplantation.[24] Immunosuppressive medications also play a role, with azathioprine and cyclosporine being most implicated.[25]

Colorectal Cancer

Colorectal cancer is the second leading cause of death from cancer in the United States. Although it remained a significant cause of death, the mortality associated with colorectal cancer declined over the last decade.[26] Colonoscopic screening allows for the detection and excision of adenomatous polyps in their slowly progressive precancerous phase. Until recently, an increased risk of colorectal cancer after transplant was not clearly established, and screening guidelines, as a consequence, were controversial.

Early studies suggested that the SIR for colorectal cancer was just under 2.[7] However, we now know that the SIR is higher than previously expected and that transplant recipients may see benefit from screening.[11] Also, in studying the frequency of EBV positivity in advanced colorectal adenomas and invasive cancer, Park and colleagues noted that these lesions are identified in younger transplant recipients at a rate comparable to nontransplanted controls of more advanced age.[11] In particular, this cohort of transplant recipients from Korea had a 12-fold increased risk of advanced neoplasia. Furthermore, the frequency of neoplasia seen in patients in their forties was comparable to patients 10 to 20 years older in the control group.[11] Using this finding as evidence, the authors concluded that colorectal cancer screening was beneficial and recommended that screening should start at a younger age than recommended for the general population.

Ano-Genital Cancer

Genital HPV infections are the most common sexually transmitted disease in the United States and are the