Malignancy Following Solid Organ and Hematopoietic Stem Cell Transplantation

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Abstract
There is a growing appreciation of the increased risk for malignancy following solid organ and hematopoietic stem cell transplantation as the survival of these patient populations increases overall. The risk for malignancy is related to a complex interaction of type, degree, and duration of immunosuppression, viral status, and recipient age. Most of the malignancies documented are common in the general population but occur with increasing incidence and have significant implications for post-transplant surveillance. Post-transplant lymphoproliferative disorder is specific to the transplant population and remains a treatment challenge. The development of novel immunosuppressive agents, the use of individualized immunosuppressive regimens, and collaborative therapeutic trials are necessary to advance clinical care for these patients. This article will review the current issues around malignancy in the post-transplant patient population.

Keywords
Solid organ transplantation, hematopoietic stem cell transplantation, malignancy, post-transplant lymphoproliferative disease

Solid organ transplant (SOT) and hematopoietic stem cell transplant (HSCT) recipients and their grafts are enjoying increased survival due to modern immunosuppressive regimens and aggressive supportive care. This success is tempered by an increasing incidence of malignancy following transplant. Malignancy is now identified among the three leading causes of mortality in the SOT population along with cardiovascular disease and infection in most registries, and is the leading cause of mortality in Australia. The cumulative risk for malignancy in renal transplant recipients reported to the United Network for Organ Sharing (UNOS) is as high as 14.9% at three years and up to 30% at 20 years following transplant. Analysis of data from the Australia and New Zealand Dialysis and Transplant Registry (ANZOT) has demonstrated malignancy rates similar to non-transplanted individuals 20–30 years of age and older. The risk for second malignancy following HSCT is increasingly recognized as a late effect and is estimated to approach 15–20% among long-term survivors.

Malignancy Classification
Malignancy following solid organ transplantation may be classified as recurrent pre-existing disease, donor-transmitted disease, or de novo disease. The risk for early and aggressive recurrence of both pre-existing recipient malignancy and donor-derived malignancy following transplantation was identified from data available from transplant registries. Clinical practice guidelines addressing wait times and screening for renal transplant candidates with a history of malignancy have been published. These guidelines may not be appropriate for non-renal allograft candidates in whom the balance of the risk of a defined waiting period and that of recurrent disease must be considered. Similarly, careful screening of potential donors for past or present malignancy is critical to avoid the relatively rare but potentially fatal incidence in a number of recipients of donor-derived malignancy. An ‘extended’ donor pool to address a growing organ shortage including those donors with a history of malignancy at low risk for transmission is a matter for debate.

The burden of malignant disease following solid organ transplantation is due to the development of de novo cancer. Registry data are somewhat variable, but suggest a two- to three-fold increased incidence after transplantation for many tumors, including the common adult carcinomas, compared with the general population. Less common tumors including melanoma, leukemia, hepatobiliary tumors, and cervical and vulvovaginal tumors are up to five-fold more common, kidney tumors up to 15-fold more common, and some tumors—including Kaposi’s sarcoma, non-Hodgkin’s lymphoma (including post-transplant lymphoproliferative disease [PTLD]), and non-melanoma skin cancers—are increased more than 20-fold.

The most commonly reported diagnoses are skin cancers (35.9%), PTLD (13.5%), and liver cancer (11.8%). By contrast, PTLD is responsible for up to 80% of
Hematological Malignancies

The risk for malignancy following transplantation is related to the type, degree, and duration of immunosuppression, viral co-factors, and recipient age. Immunosuppression interferes with normal cancer immunosurveillance and cytotoxic T-cell activity necessary for viral control.26 The extent of immunosuppression (induction and maintenance) appears to be most important clinically,27 although there is considerable evidence to support the oncogenic effect or lack thereof of individual agents.28 The greatest risk for malignancy is associated with the use of anti-T-lymphocyte immunosuppression with antithymocyte globulin (ATG) or OKT3. Less risky are azathioprine and the calcineurin inhibitors, whereas mycophenolate and the mammalian target of rapamycin (mTOR) inhibitors (sirolimus and everolimus) appear to confer significantly less risk. The anti-CD25 monoclonal antibodies (daclizumab and basiliximab) have no identified increase in risk. As expected, malignancy rates are higher in non-renal-allograft recipients, where more intense immunosuppressive regimens are required.6 The role of viral co-factors is evidenced clinically by the increased risk for cancers of known or suspected viral etiology.28 These include Kaposi’s sarcoma and human herpesvirus 8 (HHV-8), lymphomas (including PTLD) and Epstein-Barr virus (EBV), oral, genito-urinary, or skin cancers and human papillomavirus (HPV), and liver cancer and hepatitis B and C viruses (HBV/HCV).29 The risk for malignancy following transplantation is inversely related to age at transplantation,4 and pediatric transplant recipients are at greatest risk due to their often viral-naïve status and their cumulative immunosuppression.

Post-transplant Lymphoproliferative Disorder

PTLD is a spectrum of disease with a heterogenous presentation and biology, making its diagnosis and treatment particularly challenging. The World Health Organization (WHO) 2001 classification identifies four categories of disease: early lesions, polymorphic (polyclonal/ monoclonal), monomorphic (B- and T-cell lymphomas), and other (Hodgkin’s disease-like, plasmacytoma-like).21

The disease may occur at any time following transplantation and is arbitrarily defined as early when occurring less than one year and late when occurring after one year. Approximately 60% of patients will present early.26 Disease may present in the transplanted allograft of a solid organ recipient, in nodal or extranodal tissues, or in single or multiple organ sites. Disseminated disease with a fulminating clinical course has been described, particularly in the early period following HSCT.23 A full staging evaluation should be completed with attention also to the central nervous system (CNS) by imaging and diagnostic lumbar puncture. Positron emission tomography (PET) scan has been found to be useful in the detection, staging, and response evaluation of PTLD.24

In the SOT population, PTLD is primarily recipient-derived, although donor-derived PTLD within the transplanted allograft has been described.25 PTLD following HSCT is of donor cell origin.7 EBV-associated PTLD accounts for approximately 75–80% of cases and EBV-negative PTLD the remainder.26–28 The latter may be increasing in incidence29 and recent studies have challenged previous reports of late presentation and poor outcome.30–32 In an immunosuppressed host, lack of EBV-cytotoxic T-cell (EBV-CTL) activity allows for EBV-induced, uncontrolled B-cell proliferation and the development of PTLD.30,33 Both primary and latent EBV infection predispose to EBV-PTLD, with the greatest risk for an EBV-seronegative recipient with a similarly positive donor. Induction protocols for SOT or conditioning/GvHD therapies for HSCT resulting in T-cell depletion are associated with dose-related increases in EBV viral load and an increased incidence of PTLD.34–36 The exact role of EBV viral load monitoring remains unclear. The negative predictive value of EBV viral load monitoring has been demonstrated to be high; the positive predictive value is significantly lower.46 It may be useful to identify a population of transplant recipients at increased risk for de novo and recurrent PTLD.44

The use of prophylaxis against EBV infection in EBV-naïve patients has not been shown to be effective in preventing EBV-PTLD in studies to date.17–19 A strategy of decreasing immune suppression with and without the use of antiviral therapy at the time of EBV infection may be effective in reducing the incidence of EBV-PTLD.35,40 The prophylactic
and therapeutic benefit of donor EBV-CTLs in the HSCT setting and autologous EBV-CTLs in the SOT setting has been demonstrated, but remains limited as it is a resource- and time-intensive therapy. More recent studies are reporting on the successful use of allogeneic (best HLA match) EBV-CTLs in the SOT setting.

Mortality from PTLD remains high: approximately 30–40% from the disease and an additional 30–40% from treatment-related mortality. The principles underlying therapy include early diagnosis, the potential for increased toxicity from treatment in immunosuppressed patients, and the need to maintain the allograft. Reduction of immunosuppression to induce an effective T-cell response is the mainstay of therapy of PTLD. Disease response is more commonly seen with polyclonal than monoclonal disease and usually occurs within two to four weeks. Localized disease may be treated surgically. With progression of disease and/or allograft rejection, further therapy is warranted, although the extent of that therapy is debated. Currently, rituximab is considered front-line therapy for adults and chemotherapy is reserved for relapsed or refractory disease. More recently, a low-dose chemotherapy regimen was found to be effective and well tolerated for PTLD. The Children’s Oncology Group (COG) recently completed accrual to a study combining low-dose chemotherapy with rituximab for EBV-associated CD20-positive B-cell PTLD. Early treatment with rituximab in the HSCT setting should be considered. Our institutional practice is to use standard lymphoma-specific chemotherapy regimens for CNS-positive disease, EBV-negative PTLD, Hodgkin’s PTLD, and other non-B-cell PTLD histologies.

**Prevention of Malignancy Following Transplantation**

Anticipatory guidance of transplant recipients in terms of known carcinogens including sun exposure, smoking, alcohol, and diet is crucial. A number of guidelines were published addressing follow-up and screening of the transplant population and underscoring the need for increased awareness of the potential for increased toxicity from treatment in immunosuppressed patients, and the need to maintain the allograft. Reduction of immunosuppression to induce an effective T-cell response is the mainstay of therapy of PTLD. Disease response is more commonly seen with polyclonal than monoclonal disease and usually occurs within two to four weeks.

**Conclusion**

The number of individuals affected by malignancy following transplantation continues to increase. There is a need for ongoing collaborative research to further our understanding of the complex interactions between host, viral co-factors, and immunosuppressive therapies. Similarly, we have an opportunity and an obligation to advance clinical care of our transplant recipients through multi-institutional therapeutic trials. The next decade holds great promise even in the face of an increasing burden of disease.