CHAPTER 17

POST TRANSPLANT LYMPHOPROLIFERATIVE DISORDER: A RETROSPECTIVE ANALYSIS OF ANZDATA

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Introduction

Lymphomas are the third most common cancer affecting recipients of renal transplants in Australia, with a risk ratio of 9.5 over the general population. Post Transplant Lymphoproliferative Disorder (PTLD) complicates 1-10% of all solid organ transplants worldwide. Whilst the risk factors associated with PTLD have been well documented, patient survival following diagnosis is less clear.

Lymphoproliferative disorders following transplantation have markedly different characteristics compared with the general population. Extra nodal involvement is more common in the transplant population. The majority of tumours are of B cell origin and are generally large-cell lymphomas. Using the ANZDATA Registry we have retrospectively analysed data from 13,778 grafts performed in Australia and New Zealand between the years 1970 and 1999.

Although our knowledge of its pathogenesis is limited, the majority of cases of PTLD appear to be related to B cell proliferation induced by Epstein-Barr virus (EBV) infection. This combined with immunosuppression induced impairment of tumour surveillance by cytotoxic T cells, and chronic antigenic stimulation by the allograft, leads to disturbance in the normal equilibrium between cell division and death of EBV infected cells.

The major risk factors for the development of PTLD in solid organ transplant recipients include the degree of overall immunosuppression, and the presence of EBV and or CMV seromismatch between the recipient and the donor organ. Patients at risk of developing PTLD are those who have multiagent immunosuppressive regimes, particularly those that include calcineurin inhibition or those who receive antilymphocyte antibody.

Patients who are EBV naive prior to transplant and who seroconvert, carry a risk 24 times greater of developing PTLD than those who are EBV immune. CMV seromismatch confers a 4-6 fold increased risk of PTLD. In a series of 381 non-renal transplant patients seen at the Mayo clinic, the combination of an antilymphocyte antibody with a patient who was seromismatched for both CMV and EBV conferred a risk of fatal PTLD that was 654 times that of patients who had none of these risk factors.

Figure 17.1

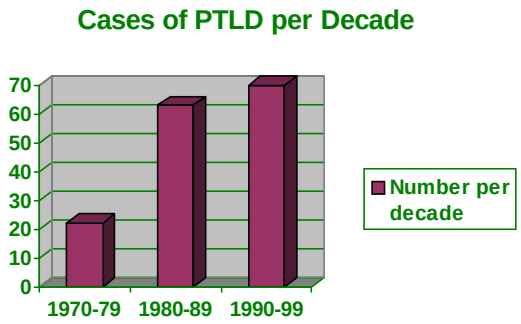


Figure 17.2

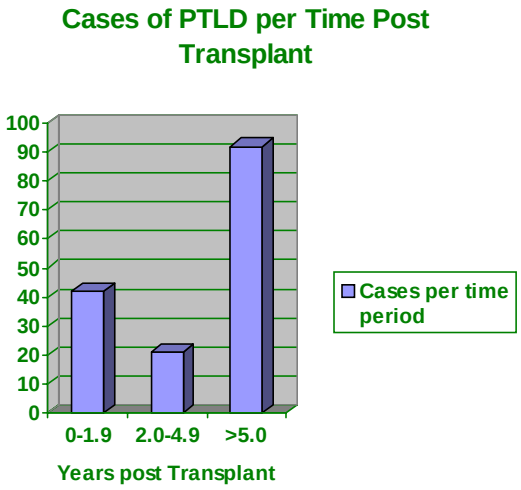


Figure 17.3

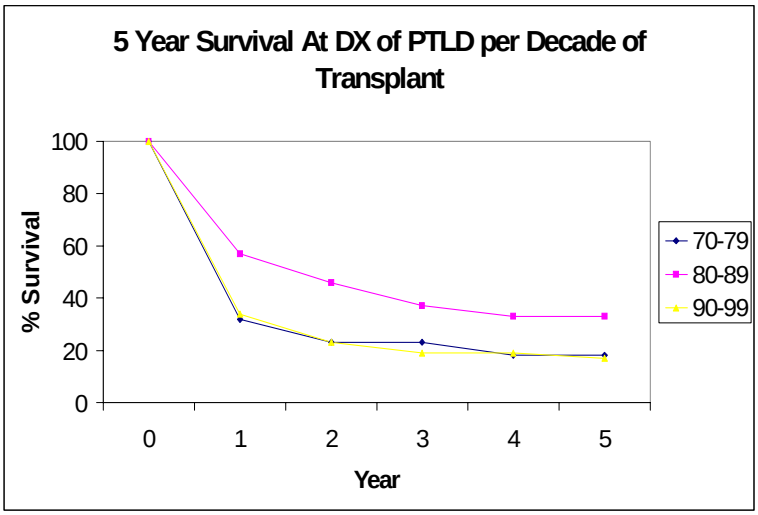
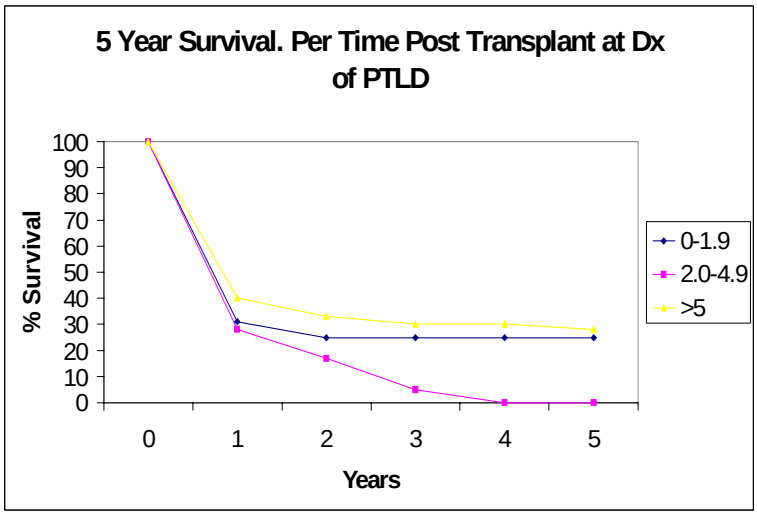


Figure 17.4



RESULTS

- 13,778 grafts were performed in Australia and New Zealand between the years 1970 and 1999.
- 155 patients developed PTLD. 57% were male.
- The mean age at transplant of those who subsequently developed PTLD was 42.8 years.
- The mean age at diagnosis of the lymphoproliferative disorder was 49.5 years.
- PTLD complicated 0.7% of grafts in the decade 1970-1979, 1.3% in 1980-1989, and 1.3% in 1990-1999 (fig 17.1)
- 26% of patients developed the disease in the period 0-1.9 years post transplant (n=42), 13% from 2.0-4.9 years (n=21), and 61% after five years (n=92) (fig 17.2).
- Five year survival for the 0-1.9 year group was 25%, and for the greater than five year group was 32%. No patients in the 2.0-4.9 year group survived five years (excludes patients lost to follow up) (fig 17.4).
- 12 month mortality rates were 62% (0-1.9 years), 62% (2-4.9 years) and 43% (>5 year group) (fig 17.4).
- Mean five year patient survival following diagnosis of PTLD was 18% in the decade from 1970 to 1979, 31% from 1980 to 1989 and 17% from 1990 to 1999 (excludes patients lost to follow up) (fig 17.3).
- 12 month mortality rates per decade were 68% (1970-79), 46% (1980-89) and 51% (90-99) (fig 17.3).

Discussion

The incidence of lymphoma in the general community is approximately 0.1%. The five year survival for lymphoma in the non transplant population ranges from 83% to 32% depending on prognostic indices. Lymphoproliferative disease in the setting of solid organ transplantation is a highly aggressive disorder with an overall five year survival rate in the Australian and New Zealand renal transplant population of 25%. Approximately half the patients who develop PTLD will die within the first 12 months after diagnosis.

The poor prognosis of patients who develop PTLD is related to their immunocompromised state, particularly impairment in T cell mediated immunosurveillance. This results in reduced effectiveness in controlling EBV infected B cells and promotion of PTLD. The reluctance of clinicians to reduce immunosuppression and risk graft loss may play a part in the poor outcomes.

Measures aimed at improving prevention strategies and subsequently reducing the prevalence of the disease are long-term goals. Reducing the burden of immunosuppression in the early and late post transplant phases are an important first step. Previous reviews have demonstrated a reduction in the incidence of PTLD with aggressive tapering of tacrolimus and corticosteroids. Early detection of EBV infection could potentially play an important role in reducing the development of PTLD. The high incidence of PTLD in EBV seromismatched recipients, and in EBV naive patients who seroconvert post transplant, suggests that early detection and treatment of EBV infection may deter the development on a monoclonal lymphocyte response. Although somewhat impractical, avoiding transplantation of an EBV positive kidney to an EBV negative recipient may reduce the risk, as would avoidance of antilymphocyte antibodies in EBV seromismatched patients.

The combination of antiviral agents active against EBV used prophylactically in high risk patients, early detection of EBV infection using polymerase chain reaction in concert with antiviral therapy and aggressive immunosuppression withdrawal protocols have shown promising results with a 50% reduction in the incidence of PTLD at one centre.

Conclusion

- PTLD is a common malignancy following transplantation, and has become more prevalent since the introduction of calcineurin inhibition.
- PTLD occurs in a bimodal distribution, with most cases occurring within the first two years after transplantation and greater than 5 years after transplantation.
- Prognosis of recipients of kidney transplants who develop PTLD is comparable to the most aggressive forms of Non-Hodgkins lymphoma in non transplant patients.
- PTLD carries a 50% 12 month mortality rate.
- Effective antiviral therapies and early detection and treatment of EBV infection may play a significant role in reducing the incidence of PTLD.
- Total dose of immunosuppression should be kept to a minimum.
- The use of monoclonal antibodies in EBV seromismatched recipients should be avoided.