POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER

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Background: Posttransplant lymphoproliferative disorder (PTLD) is increasingly recognized as a serious complication of solid organ transplantation in both children and adults. Factors associated with increased risk of PTLD include mismatch of recipient and donor EBV serologic status (seronegative recipient with seropositive donor), and intensive drug-induced immunosuppression.

Methods and results: We searched MEDLINE for articles published since 1970 to January 2009. Search terms included posttransplant lymphoproliferative disorder, immunosuppression, posttransplant malignancy, treatment, antiviral agents, rituximab, interferon alpha, chemotherapy, radiation, surgery. Studies in English of adult and pediatric populations after solid organ transplantation were selected and analyzed.

Conclusion: Screening of patients at risk and balancing the intensity of immunosuppression against the risk of allograft rejection could reduce the risk of developing PTLD. In patients who develop PTLD, the severity and extent of disease should be examined and an individualized treatment plan including immunosuppression reduction and other agents should accordingly be chosen.

INTRODUCTION

Posttransplant lymphoproliferative disorder (PTLD) is a heterogenous group of lesions occurring after solid organ and bone marrow transplantation1–5. PTLD is one of the most serious complications of chronic immunosuppression. The majority of malignant lymphoproliferative disorders occurring after solid organ transplantation are of B-cell origin but they may also originate from T-cells7–12, and extremely rarely from natural killer (NK) cells8. B-cell proliferation is predominantly induced by infection with Epstein–Barr virus (EBV) but EBV-negative disease has also been reported13. Most PTLD cells found in patients with solid organ allografts are of host origin14.

The histologic spectrum of PTLD ranges from hyperplastic lesions, which sometimes resemble infectious mononucleosis, to atypical lymphoid lesions, to lymphomas. The vast majority of lymphomatous PTLD are non-Hodgkin lymphoma (NHL)15.

The overall incidence of post-transplant lymphoproliferative disease varies from 1 to 20 percent depending on the type of organ transplanted, patient age, Epstein-Barr virus (EBV) serostatus of recipient and donor and, aggressive immunosuppression16. PTLD can develop any time after transplantation (1 month to many years), although most cases are observed in first posttransplant year. PTLD is an increasingly significant cause of morbidity and mortality. The cited mortality of solid organ transplant recipients with PTLD is 60 percent8,17.

The clinical presentation varies with constitutional symptoms of fever, malaise, an infectious mononucleosis-like syndrome, palpable lymphadenopathy and symptoms related to organ dysfunction. Histopathological evidence of lymphoproliferation on tissue biopsy is necessary to confirm the diagnosis18,19.

Survival rates depend mainly on age and extent of disease at the time of diagnosis. Pediatric patients and patients with localized disease have the best prognosis. The most aggressive are monomorphic lesions.

Treatment ranges from reduction or withdrawal of immunosuppression to chemotherapy and radiation treatment. Therapeutic approaches also include antiviral and cellular therapy.

Prior to 1981, all posttransplant lymphoproliferative disease entities were uniformly referred to as immunoblastic sarcomas. In 1981 Hanto et al.20 published their findings on a renal transplant population at the University of Minnesota of a relationship between the Epstein-Barr virus and posttransplant lymphoproliferations. At the same time Frizzera et al.21 studied tumors from a group of renal transplant recipients and posttransplant lymphoproliferations. At the same time Frizzera et al.21 studied tumors from a group of renal transplant recipients and observed several forms of lymphoproliferation that had not been described before. Given the heterogeneity in tumor cell size and shape he called them “polymorphic”. Further investigation showed that tumors are composed of B-lymphocytes. Frizzera et al.21 created a classification system which differentiated nonspecific reactive hyperplasia from polymorphic diffuse B cell hyperplasia and polymorphic diffuse B cell lymphoma and from immunoblastic sarcoma. Later Nalesnik et al.2 investigated a transplant population at the University of Pittsburg and in 1988 they set up the new classification system. As they did not discern any difference in the clinical presentation of the two types of polymorphic lesions they included them both under the term, polymorphic PTLD. To distinguish the group of lesions which resemble typical non-Hodgkin’s lymphomas
in occurrence and aggressive behavior they introduced the term monomorphic PTLD. In 1989 Locker and Nalesnik described several categories of PTLD based on combined pathologic, immunohistopathologic and molecular characteristics. In 1995 the classification system of Knowles et al. was established. There were three categories of PTLD - the first consisted of reactive hyperplasia of plasma cells, the second comprised lesions of polymorphic hyperplasia and polymorphic lymphoma, both of which were monoclonal and lacked oncogene and tumor suppressor gene alterations. The third category was formed by true lymphomas and hematopoietic neoplasms which were monoclonal and contained proto-oncogenes and/or tumor suppressor gene alterations. The Society for Hematopathology Workshop Classification in 1997 determined several distinct categories of PTLD. These included early lesions, polymorphic PTLDs, monomorphic PTLDs (B and T cell lymphomas), plasmacytoma-like lesions, and T cell-rich large B cell lymphoma/Hodgkin’s disease-like lesions. In 2001, Harris, Swerdlow, Frizzera and Knowles reviewed the classification system for the 2001 World Health Organization Classifications of Tumors. Since then the WHO Classification has remained in widest use, with the last updating in 2008.

Table 1. Posttransplant lymphoproliferative disorder (PTLD) – WHO Classification 2008.

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<thead>
<tr>
<th>M-9971/1</th>
<th>Early lesions Plasmacytic hyperplasia Infectious mononucleosis-like PTLD</th>
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<tr>
<td>M-9971/3</td>
<td>Polymorphic PTLD</td>
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<td>Monomorphic PTLD (B and T/NK cell types)</td>
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<td>Classical Hodgkin lymphoma type PTLD</td>
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PATHOPHYSIOLOGY

Most cases of PTLD are associated with EBV infection from B-lymphocytes, which in the setting of immunosuppression, can induce a transformation to a lymphoproliferative disorder. EBV is a herpes virus that is found in the oropharyngeal tissue of nearly 95 percent of the adult population. A primary infection with EBV is typically acquired during childhood through infected saliva, via breast milk, or as an infectious mononucleosis. The majority of primary EBV infections are subclinical while in adults the clinical syndrome of infectious mononucleosis may be present. It has been estimated that approximately 90 percent of the global population harbor EBV by the age of 40. Structurally, the EBV virus is composed of the EBV genome and nuclear capsid surrounded by a glycoprotein envelope. The CD21 molecule on the surface of the B cell is the target receptor of the EBV glycoprotein envelope. During primary infection, EBV incorporates into B-lymphocytes which transform and immortalize. Once a person is infected with EBV, the virus persists for life as a result of latency. Latent EBV infection is associated with a number of different malignancies, including PTLD, HIV-associated lymphomas, endemic Burkitt’s lymphoma, and a subset of Hodgkin’s lymphoma. In PTLD, EBV-latent membrane protein 1 (LMP1) has been implicated in the transformation of B-lymphocytes through a receptor in the tumor necrosis factor receptor family. The B cell transformation is associated with activation and continuous proliferation. In immunocompetent individuals, the proliferation of B-lymphocytes is controlled by means of CD4 and CD8 cytotoxic T cells and natural killer (NK) cells. However, in patients who are immunosuppressed, the T cell function is inhibited and EBV induces uncontrolled B cell expansion. In initial stages, the proliferation is polyclonal. With mutation and selective growth, the lesions become oligoclonal and, later, monoclonal.

Patients who are EBV negative and receive grafts from EBV-positive individuals are at highest risk for developing PTLD. In this situation the EBV virus is transmitted from donor to recipient via the graft at the time of high immunosuppression for the recipient. For instance, in Cockfield’s 1993 analysis it was found that the incidence of PTLD in patients who were EBV seronegative pretransplant was significantly higher than those who were seropositive (23.1% vs. 0.7%). In another study from the Mayo Clinic of 381 adult nonrenal transplant recipients, the rate of developing PTLD was 24 times higher in EBV-negative than in EBV-positive recipients.

PTLD that is not associated with EBV infection is less understood. Tumors not due to EBV also present a number of different patterns. As reported in one French study, they develop much later (2324 vs. 546 days post-transplant).

CLINICAL PRESENTATION AND DIAGNOSIS

The clinical presentation of PTLD is highly variable. Some patients remain symptomless, in others, early symptoms can be nonspecific, such as fever, malaise and weight loss. Sometimes, the features resemble those of infectious mononucleosis, especially in children. Most lymphomas typically involve lymphnodes, however, extranodal involvement is also common. As PTLD can assume a number of guises, a high degree of clinical vigilance is required if the diagnosis is not to be missed. In all transplant recipients with a fever of 3 days or more, clinical suspicion for PTLD increases. A routine examination including laboratory tests and imaging studies, and lymph node excision is required to diagnose PTLD. Tissue biopsy is needed to determine PTLD histology. Immunohistology staining and serum PCR examination can be used to confirm the presence of EBV infection. EBV viral loads in the peripheral blood can be measured using EBV polymerase chain reaction (PCR). In situ hybridization with the EBV-encoded RNA probe can detect EBV in tissue.
INCIDENCE

PTLD incidence varies according to the type of organ transplanted. An overall incidence of lymphoproliferative disorder approximately 30 to 50 times higher than in general population has been reported. PTLD is most common in intestinal or multorgan transplant recipients where the incidence ranges from 11 to 33 percent. In lung transplants it is 2 to 9 percent from 2 to 6 percent in heart transplants and from 1 to 3 percent in liver transplants. The lowest PTLD incidence occurs in renal transplants with approximately one percent of the recipients being affected. These findings suggest that PTLD incidence almost certainly reflects the need for more intensive immunosuppression in non-renal transplant recipients.

As shown in multiple studies, solid organ transplant patients at increased risk for PTLD are those treated with more intensive immunosuppression, especially those exposed to certain types of induction therapy. In addition, the amount of lymphoid tissue that is transferred at organ transplantation increases the PTLD risk, as this transferred lymphoid tissue serves as reservoir for viruses such as EBV and Cytomegalovirus (CMV).

Age also carries a significant PTLD risk. Data from the IPITTR suggest that pediatric patients have a higher incidence of PTLD than do adults (53% vs. 15%, respectively). The rationale for this finding from a large number of studies is that, unlike adults, many pediatric patients have never been exposed to viruses such as EBV by the time of transplantation.

PREVENTION

Reducing risk factors in organ transplant recipients seems to be the best strategy for preventing PTLD. The principal risk factors underlying the development of lymphoproliferative disorder post-transplant are the degree of overall immunosuppression and EBV serostatus of the recipient. An anti T cell immunosuppressive agent, a calcineurin inhibitor (cyclosporine or tacrolimus), an antiproliferative agent (mycophenolat mofetil, sirolimus or azathioprine), and corticosteroids are used to prevent organ rejection. Hence intense immunosuppression facilitates PTLD development. It is thus important to use the smallest combination and the lowest doses of required immunosuppressives. Owing to the strong relationship between EBV and PTLD, screening for EBV infection and the use of antiviral agents may be beneficial.

The American Society of Transplantation recommends monthly EBV monitoring for the first posttransplant year in EBV-mismatched individuals. The polymerase chain reaction (PCR) can detect changes in the EBV viral load over time, allowing for early detection of first-time EBV infections and EBV reactivation. The effectiveness of both prophylactic use of antiviral agents and the early detection of primary EBV infection with PCR followed by antiviral therapy and immunosuppression reduction was evaluated in 40 children receiving a liver allograft. The result suggests that aggressive preemptive therapy and frequent monitoring for early EBV infection, which (when detected) is managed by intravenous ganciclovir and reduction of immunosuppression, may lower the incidence of PTLD.

In a retrospective multicenter case-control study of renal transplant recipients Funch et al reported that prophylactic antiviral therapy reduced the risk of PTLD. In this report of 100 biopsy-confirmed cases and 375 controls, the risk of PTLD during the first posttransplant year decreased by 38 percent for every 30 days of treatment with ganciclovir (OR of 0.62, 95% CI 0.38–1.03). The specific antiviral agent to use is also a subject for discussion. The data suggest that ganciclovir may be more beneficial than acyclovir in reducing the PTLD risk. In the case-control study conducted by Funch et al. (n=100 PTLD cases), for every 30 days of ganciclovir treatment, the risk of developing PTLD in the first year was decreased by 38 percent compared with only 17 percent risk reduction by using acyclovir.

TREATMENT

In 1984, Starzl et al were the first to suggest reduction or withdrawal, of immunosuppression as a treatment option for PTLD. In immunocompetent individuals there are potent mechanisms of both humoral and cellular immunity (esp. CD4 and CD8 cytotoxic T cell and natural killer cells) which work well to prevent the outgrowth of EBV-infected lymphocytes. Thus reduction or withdrawal of immunosuppression serves to allow patients' natural immunity to recover and gain control over the proliferating EBV-infected cells again.

The majority of polyclonal lymphoproliferative disease lesions either resolve completely or improve significantly with only reductions of immunosuppression. EBV-related plasmacytomas may also disappear after reduction of immunosuppression. For example, Benkerrou et al. reported complete regression in 40 percent of patients after reduction or discontinuation of immunosuppressive therapy. In Cohen’s review, two thirds of transplant recipients with PTLD whose cases were managed with reduction of immunosuppression survived, compared with an overall survival rate of 31% (ref.). Currently there is a general consensus that immunosuppression should be reduced or withdrawn in cases of PTLD in the first instance, however, no strict guidelines exist for this process. Hence the specific decision rests in the hands of the clinician who must consider the risk of allograft rejection after drug dose reduction or withdrawal. The aim is to achieve a balance – to improve immune function to gain remission from lymphoproliferation while at the same time preserving the allograft.

Different immunosuppression reduction regiments have been tried based upon the severity of PTLD. Among those with only limited disease, one regimen is the reduction by at least 50 percent of cyclosporin (or tacrolimus) and prednisone, and discontinuation of azathioprine or mycophenolat mofetil. After two weeks, another 50 percent reduction of immunosuppression can be considered if necessary.
The results of these authors indicate that for localized PTLD both immunosuppression reduction alone and immunosuppression reduction combined with surgical excision are effective PTLD treatment. In a retrospective study of 42 adult transplant recipients with PTLD, cohorts were treated with either immunosuppression reduction alone (n=30) or immunosuppression reduction plus surgical removal of all lesions (n=12). Overall, 31 (74 percent) achieved complete remission. Among those treated with reduced immunosuppression alone, 63 percent had a complete or partial response rate within a median of 3.6 weeks after initiation. All 12 patients with localized PTLD who received surgery and reduced immunosuppression had complete response following surgery, with no relapses.

A reduction in immunosuppressive therapy is not effective for central nervous system PTLD. CNS disease requires intrathecal therapy because intravenous chemotherapy and monoclonal antibodies do not cross the blood-brain barrier adequately64. Involved field radiation therapy may be beneficial for patients with CNS involvement65, and for those with localized disease66. Surgical management may also be useful, especially for the treatment of localized complications of the disease. In Cohen’s review, survival rates of the order of 74 percent were noted for patients treated by surgical excision of the lesions, compared with an overall survival rate of 31 percent65.

T cell PTLD usually is not associated with EBV infection and does not respond to immunosuppression dose reduction52. Patients with more extensive disease but without critical illness should undergo a reduction in immunosuppression by either maintenance of steroid therapy only or decrease in calcineurine inhibitor dose by at least 50 percent and discontinuation of other immunosuppressants68. For such patients adjunctive therapy consisting of addition of rituximab or chemotherapy may be useful. Rituximab is a monoclonal anti-CD20 antibody, which has been used to treat B cell non-Hodgkin lymphoma. Its effectiveness in PTLD treatment has been demonstrated in multiple studies. For example Milpied et al.69 in France reported promising results with response rates of 65 percent in patients with PTLD treated with rituximab following solid organ transplantation. In Choquet’s prospective study of 43 patients with previously untreated B cell PTLD not responding to immunosuppression reduction, rituximab was administered for four weeks at a dose of 375 mg/m² per day for at least 80 days and one year, respectively70.

Unfortunately, there are cases in which a patient does not respond to rituximab; in such a setting, chemotherapy is the next practicable option. One primary chemotherapy regimen used is CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) regimen. Its effectiveness has been shown in several studies with the remission rates of 69% achieved among patients with B cell tumors7172. Similarly, Trappe et al. reported an overall response rate of 70% after CHOP administration among patient with refractory or relapsed disease after treatment with rituximab73. In some reports, ProMACE-CytaBOM regimen was also effective for the posttransplant lymphoproliferation treatment74. The dose of doxorubicin in ProMACE-CytaBOM is half that used in CHOP, making ProMACE-CytaBOM less cardiotoxic and possibly a more attractive regimen. However, the complications associated with chemotherapy are not advantageous and therefore chemotherapy should be used as salvage therapy in patients who fail treatment with rituximab75. Patients who have diffuse PTLD involvement have a much lower response rate to treatment regiments. Additionally because these patients are critically ill, reduced immunosuppression, rituximab, or chemotherapy may lead to life-threatening complications. Currently, recommendations for these patients are limited and the outcome is dismal.

In addition to the agent previously discussed, there is some evidence that the use of antivirals, interferon-alpha or intravenous immunoglobulins may have benefits for patients with PTLD.

As with antiviral use in prevention, mainly ganciclovir and valganciclovir are used in EBV-positive PTLD treatment76. Although there is widespread use of antivirals, no convincing rationale is provided for the efficacy of antiviral therapy in PTLD treatment. EBV PTLD arises from B cells transformed by EBV in which EBV survives as an episome outside the lymphocyte genome. In vivo, antivirals inhibit the replication of linear EBV DNA but are ineffective against episomal DNA which is the conformation of the EBV genome in latent B-lymphocyte, and so does not prevent their proliferation. Therefore antiviral agents are not recommended as the sole treatment of PTLD.

Interferon-alpha is a drug with antiviral and antiproliferative activity77 and it also inhibit T-helper cells, which release cytokines (IL-4, IL-6, IL-10) that promote B-cell proliferation78. However, its use for PTLD treatment also remains controversial. To date no prospective clinical trials have been conducted and most of the reports of its success are anecdotal. The largest series described 14 solid organ transplant recipients with systemic PTLD who were treated with interferon alpha (3 million units/m² per day for at least three weeks), combined with immunosuppression reduction. Eight patients achieved total disease regression. The therapy was continued for 6 to 9 months. None of patients had a relapse with the same neoplastic clone but 2 developed a new neoplastic clone79. Intravenous immunoglobulin (IGIV, IVIG) has been successfully used as adjunctive therapy in the management of PTLD in combination with other modalities, mainly with interferon-alpha79.

New immune-based strategy for PTLD treatment is based on the fact that EBV specific cytotoxic T lymphocytes have the ability to recognize and destroy EBV-infected B cells. Since the technology to stimulate autologous EBV-specific cytotoxic T lymphocytes (CTL) ex vivo is now available, treatment of PTLD that is of recipient origin includes transfer of ex vivo generated recipient’s EBV-specific cytotoxic T lymphocytes. As shown in one survey of clinical results, adoptive therapy with EBV-specific CTL is safe, well tolerated and particularly effective80.
CONCLUSIONS

Transplantation and the accompanying drug-induced immunosuppression put patients at risk for potentially fatal infection and malignancy. As the number of transplant recipients increases and the life expectancy of transplant recipients improves, increased rates of PTLD and other malignancies are anticipated. Among those who are in a high risk of developing PTLD are EBV-seronegative patients, nonrenal transplant recipients, patients with intense immunosuppression management, and children. To prevent PTLD, minimizing the immunosuppression burden, regular PCR EBV screening and use of antiviral agents appear to be useful strategies. PTLD treatment includes lowering of immunosuppression, antiviral therapy, surgical support, chemotheraphy, radiation and cellular therapy. However, the optimal therapy strategy still remains to be determined. There is still a great necessity for prospective randomized clinical trials to test the effectiveness of current strategies. Productive areas of investigation include: identifying patients who will benefit from reduction of immunosuppression only; improving methods for predicting those at highest risk of PTLD; developing safe and effective pre-emptive therapies; and developing more effective, less toxic therapies for resistant or aggressive disease.

REFERENCES


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69. Milpied N, Vasseur B, Parquet N, Garnier JL, Antoine C, Quartier


