Lymphoproliferative disease post-renal transplantation

Charles G. Newstead

Department of Renal Medicine, St James’s University Hospital, Becket Street, Leeds, UK

Introduction

Solid organ transplant recipients are at a greatly increased risk of lymphoproliferative tumours. The majority is of B cell origin and has been shown to contain the Epstein-Barr virus (EBV) genome and express viral proteins on the cell surface. The virus attaches to the C3d complement component receptor so effects are confined to cells that carry this receptor. These are squamous epithelial cells of the oropharynx and B-lymphocytes. In the latter cell a latent infection occurs. The virus has the capability of transforming these cells into continuously growing immortalized lymphoblastoid lines.

Incidence and risk factors

The incidence of post-transplant lymphoproliferative disease (PTLD) in renal transplant recipients is of the order of 1% [1]: a risk of lymphoma approximately twenty times greater than that seen in the general population. The major risk factor for PTLD in solid organ transplantation is the degree of immunosuppression. A high incidence of PTLD was seen following the introduction of cyclosporin A, which was greatly reduced after drug level monitoring became widespread and dose reduction occurred to about one fifth of that initially used [2]. The incidence of PTLD with tacrolimus is probably comparable to that seen with cyclosporin A [3]. The risk is much increased following antibody treatment [1].

The therapeutic suppression of natural cytotoxic T-cell activity is likely to be the cause of uncontrolled EBV-driven proliferation of B-cells [4]. Initially, polyclonal expansion would be expected but single clones with a growth advantage will predominate as time
passes. Cyto-megalo-virus (CMV) disease increases the risk of subsequent PTLD approximately 7-fold in liver transplant recipients [5]. The primary infection that is seen in a sero-negative recipient of a sero-positive graft is an important risk factor for PTLD with a relative risk ratio of 76-fold increased in that situation; this is a particular problem in paediatric practice [6].

The modes of clinical presentation

PTLD is heterogeneous, but most cases can be divided into one of four syndromes. An acute infectious mononucleosis-like disease with marked constitutional upset and rapid enlargement of tonsils and cervical nodes is the most typical pattern in the first year post-transplantation. A fulminant presentation can occur within weeks of transplantation and presents with widespread infiltrative disease with multi-organ involvement with a grave prognosis. The first two presentations are more common in young recipients who are sero-negative and receive a sero-positive organ. Isolated or multiple tumours, the latter often involving the allograft and on occasions mistaken for rejection, are usual more than 1 year post-grafting. The presentation is usually of indolent disease and visceral, nodal, and extra-nodal tumours are the rule. Gastrointestinal involvement is relatively common, as are pulmonary nodules; the lung may be the only site involved. EBV-negative B cell PTLD occurs in approximately 10% of cases. This is usually of late onset and clinically resembles non-Hodgkin’s lymphoma.

Clinical features do not correlate with the histological classification. As more sensitive techniques have been employed it has been appreciated that tissue found to be polyclonal by immunophenotyping contains monoclonal sub-populations [7]. Similarly, as techniques have improved, the percentage of tumours shown to contain EBV has increased. The pathology and classification have recently been reviewed and summarized [8].

Managing the patient with PTLD

In children receiving orthotopic liver transplants reactivation of EBV may be coincident with PTLD. However, a large proportion, perhaps as much as 90%, of PTLD in the first year is triggered by a primary EBV infection that occurs within 4 months of a sero-negative recipient receiving a sero-positive graft [9]. Where possible avoiding such mismatches, especially in high-risk groups, is a sensible tactic. There has been recent research aimed towards achieving a vaccine directed against an envelope glycoprotein (gp340) [10] and a latent membrane protein [11].

The mainstay of management is the drastic reduction or cessation of immunosuppressive treatment [12]. This allows the recovery of the recipient’s cytotoxic T-cell-directed EBV surveillance mechanism. In renal transplantation withdrawal of azathioprine or mycophenolate is advised, as is the reduction of prednisolone to approximately 10 mg per day. Cyclosporin A or tacrolimus can be reduced in a step-wise fashion by about one fifth every 2 weeks. Patients need to be closely monitored, both for evidence of graft rejection as well as tumour growth or regression. It is common to stop cyclosporin A or tacrolimus dose reduction when approximately 30% of the initial dose is reached.

Remission has been achieved with interferon alpha in a number of cases [13] but as the treatment regimens are complicated and the number of patients treated small it is difficult to be sure of the value of this approach.

Recently there have been efforts directed towards estimating viral load. Because of technical considerations there is particular interest in quantifying EBV DNA in serum rather than peripheral blood lymphocytes and a sensitivity of 83% and specificity of 100% for one such test has been reported [14]. Given that the rise in EBV viral load can be detected by serial measurements prior to PTLD, there is interest in monitoring, allowing pre-emptive prophylaxis and avoiding PTLD. Unfortunately the optimal prophylactic strategy is far from clear. The reliability of viral load estimation to aid the fine adjustment of immunosuppressive medication is yet to be determined. In particular, the author’s point out that rebound of the viral load is common but relapse of PTLD relatively rare at less than 10% [15].

Although intravenous gancyclovir or acyclovir will inhibit the lytic phase and decrease the degree of oropharyngeal shedding of virus [16], the number of EBV infected cells in peripheral blood is not altered by acyclovir treatment [17]. The anti-viral drugs only inhibit lytic infection and typically only about 1% of the cells infected are in a lytic phase. Anti-viral drugs would not be expected to influence the immortalized B-cells that are responsible for the PTLD syndrome. Consistent with this is the observation by several authors that viral loads increase while patients are receiving acyclovir or gancyclovir [17]. However, it is possible, but unproven, that inhibiting the lytic phase may influence progression of PTLD. Acyclovir, valacyclovir and gancyclovir have only weak, foscarnet good, cidovir high in vitro activity against EBV. Anti-viral drugs that are active against CMV may have some effect in PTLD as CMV produces B-cell stimulating cytokines. The literature on anti-viral treatment in PTLD has recently been reviewed [18], but the reports are confused and the drugs appear to offer relatively little anti-tumour effect. Unlike non-Hodgkin lymphoma in general, PTLD can be cured by surgical excision or irradiation of strictly localized lesions. This approach should be considered in these circumstances [19]. Another approach is to use passive immunization with anti-EBV antibody [20]. Anti-B-cell monoclonal antibodies are an attractive treatment option and were found to be successful in a European multi-centre trial [21]. They are not immunosuppressive; the antigens targeted are such that they deplete the EBV infected cell pool and these cells are then lysed by antibody
dependent cellular cytotoxicity. The original European studies used anti-CD21 and anti-CD24, which are no longer commercially available. Approximately 50% of patients developed anti-mouse antibody and this presumably will limit efficacy in the medium term. More recently an anti-CD20 antibody has undergone commercial development for use in indolent B-cell lymphomas. The published experience in PTLD is as yet scanty [22]. The best strategy for its use and how it integrates with other treatment modalities is yet to be determined. Of interest is the experience of four patients with EBV associated PTLD who were treated by autologous lymphokine-activated killer cells expanded ex-vivo by interleukin-2 [23], an approach which at present is experimental. The use of recipient cytotoxic T-lymphocytes that are stimulated in the same way as is used for the bone marrow donors [24] is in its early stages. For practical reasons peripheral white blood cells taken at the time of the diagnosis of PTLD are used and after approximately 30 days of cell culture and purification are available for infusion. The dose schedule and efficacy has yet to be reported. Another experimental approach is to use a bank of blood donors of known HLA type and generate cell lines of cytotoxic T-lymphocytes. The idea would be to try to match the HLA type of a recipient with PTLD to the bank and select a cell line that achieved good killing of the tumour cells but little (non-specific) killing of the patient’s white blood cells [20].

Conclusion

In summary, the majority of PTLDs in solid organ transplantation are due to EBV driven recipient B-lymphocyte proliferation. Sero-negative recipients of sero-positive organs, and recipients receiving anti-T cell sero-therapy are at increased risk. The measurement of viral load appears to be of little use in predicting disease. The mainstay of treatment is immunosuppressive dose reduction. Anti-viral drug therapy has at present only been shown to be of very limited benefit and there are theoretical reasons why it may be ineffective. Monoclonal antibodies directed against cells expressing CD20 are safe and a promising treatment strategy. A variety of ways of generating cytotoxic T-cells are at present in development and may be of clinical use in the future.

A review summarizing two international meetings on this topic has recently been published [25]. The authors emphasize both areas of agreement as well as gaps in our knowledge. The development of a database to properly assess the value of novel therapeutic approaches will not be easy given the small number of patients involved, and is likely to require a collaborative effort between transplant centres in more than one country.

References

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