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## Post Transplant Lymphoproliferative Disorders After Liver Transplantation

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### 1. Introduction

Post-transplant lymphoproliferative disorder (PTLD) is a clearly recognized and potentially life threatening complication after solid organ or bone marrow transplantation. It comprises a spectrum of diseases ranging from infectious mononucleosis and lymphoid hyperplasia to highly aggressive lymphoma. The disease has increased clinical importance in view of the constantly rising number of organ transplant recipients and the development of more potent and specific immunosuppressive drugs.

PTLD is a relatively common malignancy after transplantation with a reported incidence ranging from 2% to 10%. It is the most common form of post-transplant malignancy after skin cancer with an overall mortality often exceeding 50%.

Registry-based reports however usually do not provide details of treatment and outcome: the existing single institution studies are largely reports and only a few studies include a significant number of patients with PTLD. Most cases of PTLD are associated with Epstein Barr virus (EBV) that leads to uncontrolled B cell proliferation in patients with a decreased function of EBV specific T cell because of immunosuppressive drugs. PTLD is not exclusively associated with EBV infection as EBV-negative PTLD, often developing late after transplantation.

Post transplant lymphomas differ from lymphomas in general population in histopathological findings, increased extranodal involvement, a more aggressive clinical course and poorer response to conventional treatment.

Treatment of PTLD consists always in reduction of immunosuppression (RI) as first step. The role of chemotherapy (CT) remains unclear. In the past it was reserved for patients in whom other treatment options have failed even if the increased toxicities from cytotoxic agents, the high susceptibility to life-threatening infections and the necessity to maintain the allograft. Actually (Rituximab Hera) most authors consider new anti CD20 monoclonal antibodies (mAB) essential for treatment or as single agent or in association with CT but there is not a definitive agreement about schedules, duration of treatment and setting of patients.

## 2. Pathogenesis

The appearance of PTLT is often associated with clinical or serological reactivation of Epstein Barr virus infection. Tumour tissues often contain EBV-DNA sequences and express viral protein (Purtilo DT, 1980; Young L et al, 1989; Hanto DW et al, 1981). In normal individuals, host defence mechanism make EBV infection a self limited disease and B cell proliferation is controlled by specific T cell lymphocytes. The infection is however not eradicated, but persists in clinical latent form. In transplanted patients, partial suppression of T lymphocyte to prevent graft rejection, makes EBV-driven B cell proliferation uncontrolled and predispose to development of PTLT.

Several single centre studies have found that EBV seronegative patients had a 10-76 times greater incidence of PTLT than EBV seropositive recipients (Walker RC et al, 1995).

Active viral replication in immunosuppressed patients results in the expression of EBV encoded genes including oncogenes as LMP1, a gene that inhibits apoptosis by up regulating the anti-apoptotic gene BCL-2 (Kulwichit W et al, 1998).

Data suggests also that prophylactic anti-Cytomegalovirus (CMV) immunoglobulin prevent the development of early post-transplant non Hodgkin lymphoma while prophylactic treatment with antiviral drugs does not reduce the risk of PTLT (Opelz G et al, 2007).

Locker and Nalesnick (Locker J & Nalesnick M, 1989) demonstrated that monomorphic PTLTs display a strong clonal immunoglobulin rearrangement band on Southern Blotting and a c-myc gene rearrangement exhibits disease progression. Also alterations of p53 and N-ras seem to be implied in pathogenesis of PTLT. BCL 6, that encodes a transcriptional repressor gene rearranged in 35-40% of diffuse large B cell lymphoma in immunocompetent patients (Bastard C et al, 1994; Lo Coco F et al, 1994), presents frequent somatic mutations in PTLT representing probably a consistent step in the progression from a PTLT that can be controlled by a reconstituted immune system to one that will require more aggressive therapeutic intervention (Cesarman E et al, 1998).

PTLT also have genomic aberration common to lymphomas in immunocompetent patients such as gain of 8q24, 3q2718q21 and loss of 17p13.

In conclusion viral oncogenes, impaired immune system, chronic antigen stimulation and genetic aberration probably contribute together to pathogenesis of PTLT (Poirel HA et al, 2005).

## 3. Risk factors

The most important risk factor for PTLT development is the intensity of immunosuppression administered. Induction and rejection treatment with anti-T cell antibodies, especially OKT3 and ATG may lead to an increased risk of PTLT, as demonstrated by the higher incidence of early PTLT in heart and heart/lung recipient. With longer follow-up, is now evident that antibody prophylaxis increased the risk of lymphoma primarily during the first post-transplant year, whereas in subsequent years the risk is similar to that in non antibody-treated patients. Whether IL2 receptor blocking monoclonal antibody, which was introduced in the late 1990s, also increases the risk of lymphoma is of great interest. Analysis of the critical 12-months data showed that use of

anti IL2 receptor antibodies was not associated with an increased risk of lymphoma (Opelz G et al, 2003).

There is no conclusive evidence that development of PTLT is associated with a single immunosuppressive agent (Gao SZ et al, 2003; Pirsch JD et al, 1997; Weisner RH et al, 1998; Younes BS et al, 2000). Also the effect of everolimus and sirolimus on PTLT development is not clear. These drugs may theoretically be associated with a lower risk as demonstrated in animal model but the lack of prospective randomized trial assessing these differences restrains any firm conclusion (Yakupoglu YK et al, 2006; Majewski M et al, 2003; Kusuki S et al, 2009).

A special category of patient at risk (10 to 50 fold increased risk) are EBV seronegative patients receiving allograft from EBV seropositive donors, leading to primary EBV infection (Walker RC et al, 1995). This is also the reason for the higher incidence of early PTLT observed in paediatric transplant recipients who often are still EBV seronegative at the time of transplantation.

A high incidence of EBV related lymphoproliferative disorders has been reported in a number of congenital immunodeficiency syndromes including severe combined immunodeficiency (SCID), ataxia teleangiectasia and Wischott Aldrich syndrome Waldmann TA et al, 1983). Acquired immunodeficiency due to HIV disease has become a major clinical problem in many parts of the world. An increased incidence of aggressive non Hodgkin lymphoma which shares many of the unusual characteristics of PTLT is a manifestation of AIDS. The introduction of the Highly Active Antiretroviral Therapy (HAART) has dramatically reduced the incidence of this life threatening manifestation of HIV.

The underlying indication for transplantation may also influence the risk for PTLT. For example Hepatitis C infection (Burra P et al, 2006) is associated with a particularly high risk of PTLT in liver transplant recipients.

Recent data also suggest Hepatitis B virus reactivation as a possible risk factor for development of PTLT (Leblond V & Choquet S, 2004; Duvoux C et al, 2002; Zhang A et al 2009).

Also patients with immunological disorders before liver transplantation receiving steroids and patient transplanted for autoimmune hepatitis seems to be at higher risk for development of PTLT (Zimmermann T et al, 2010; Shpilberg O et al, 1999)

#### 4. Epidemiology

The incidence of PTLT after solid organ transplantation is different in children and adults and varies according to the type of organ transplanted.

The incidence is significantly higher in paediatric recipients and has been reported in 1-10% of kidney or liver transplants and 6-19% of heart, lung and heart and lung transplants. However the true incidence of PTLT in adult and paediatric recipients is difficult to determine with accuracy (Leblond V & Choquet S, 2004; Patel H et al, 2007).

PTLT is surprisingly uncommon (<1 %) in the setting of allogeneic bone marrow transplantation in the absence of specific T-cell manipulation such as use of a monoclonal

anti CD3 antibody or T cell depletion of donor marrow. The incidence of PTLD would be expected to increase with the duration of immunosuppression and few studies standardise their data on incidence for this variable. Also the lack of standardised diagnostic criteria for PTLD may reflect the wide range in incidence.

Although PTLD may occur at any time after transplantation, the risk of developing PTLD is greatest within the first year and declines over time thereafter. A report by the Transplant Collaborative Study showed the incidence of PTLD to be 224/100000 in the first year, 54/100000 in the second year and 31/100000 in the sixth year following transplantation<sup>11</sup>.

The higher incidence of PTLD in paediatric transplant recipient is attributable in large part to the development of primary EBV infection after transplantation. EBV seronegative adults who acquire primary EBV infection after transplantation are also at increased risk of PTLD but since most adults are already EBV seropositive at the time of transplantation this is a less problem.

In both children and adult, PTLD is more common after heart and lung transplantation than after kidney or liver transplantation. This may be because more intensive immunosuppression is used in recipient of thoracic organ. In lung recipient the large number of EBV-infected lymphocytes residing in lung transplants in the form of bronchus associated lymphoid tissue may be a contributing factor in EBV seronegative recipients.

## 5. Pathologic features

A standardised approach to the classification of PTLD is important to allow consistency of reporting and to enable comparison of different treatments. Histology is essential also in differentiation between rejection and PTLD involvement of the graft. The classification of PTLD currently used is based on the histopathological appearance of the tumour. PTLD can be divided into three distinct morphological groups, as reported by the World Health Organization classification of neoplastic disease of the haematopoietic and lymphoid tissues.

The first group comprises diffuse B cell hyperplasia, characterised by differentiated plasma cell and preservation of the normal lymphoid architecture. This type of PTLD is most often seen in children and young adults, usually occur within the first year following transplantation and responds well to reduction of immunosuppression (Kahan BD et al, 2000).

The second group comprises polymorphic PTLD characterised by nuclear atypia, tumour necrosis and destruction of underlying lymphoid architecture. Lesions in this group are highly polymorphic, usually monoclonal and include plasmacytes and blast form. Polymorphic PTLD is the most common type of PTLD in both children and adults and may occur at any time after transplantation.

The third group comprises monomorphic PTLD and includes high grade invasive lymphoma of B or T lymphocytes. This type of PTLD is often seen several years after transplantation and resembles non Hodgkin lymphoma. Monomorphic B cell PTLD can be further divided into diffuse large cell lymphoma and Burkitt or Burkitt like lymphoma. PTLD may also present with discordant lesions, in which different histological subtypes can be present in a single patient.



Although the association between EBV and PTLD is well established, the presence of EBV in tumour cell is not required for the diagnosis. So, according to the international classification, any lymphoma arising in the post-transplant patient is considered to be a PTLD.

At least 90% of PTLD that occur in solid organ transplant patients arise from recipient cells (Weissmann DJ et al, 1995) and the opposite apply in the case of bone marrow transplantation. Donor derived PTLD in organ transplant patient may have a predilection for the allograft (Strazzabosco M et al, 1996). Some authors have suggested that they may have a worse and some a better prognosis than recipient organ PTLD even if further studies are needed in this area (Lones MA et al, 1997; Howard TK et al, 1992).

Clinical recurrence of PTLD has been estimated to occur in approximately 5% of cases. Wu et al.<sup>30</sup> (Wu TT et al 1996) examined a series of 11 such patients and found that the recurrent tumours comprised a heterogeneous assortment. In some cases the recurrence was morphologically and clonally identical to the original tumour. In several cases PTLD recurred in a more aggressive form. For example, patients with mononucleosis-like PTLD could present later with polymorphic PTLD, and patients whose original disease was polymorphic PTLD might later develop one of the lymphomatous forms of PTLD.

## 6. Clinical presentation

The clinical presentation of PTLD is highly variable. PTLD may arise at any time after transplantation with a significantly higher risk in the first post-transplant year, especially in heart and lung recipient because of the high dose of immunosuppression. Most patients present with fever (seen in 50%), lymphadenopathy (seen in 30%) or non-specific symptoms such as tonsillitis (particularly children) and weight loss. Around 15% of patients present as an emergency with intestinal perforation (Kahan BD et al 2000) or with fulminant PTLD characterised by disseminated systemic disease that clinically resembles septic shock (Orjuela M et al, 2003). Keeping in mind that PTLD often present at extra nodal sites (Bakker NA et al, 2005), including the allograft and digestive tract, there may be early signs and symptoms that should at least include PTLD in the differential diagnosis. This is especially true for allograft involvement of PTLD. The most commonly affected extranodal site of PTLD is observed in the gastrointestinal tract (G.I.). There seem to be no relation between the time of onset and the development of PTLD in the G.I. tract (Leblond V et al, 1995). The CNS is involved in up to 30% of cases of PTLD and in many of these the disease is confined to the CNS (Maecker B et al, 2007; Penn I & Porat G, 1995). In this respect, PTLD contrasts with NHL in the general population where only around 1% of cases shows isolated CNS involvement. Skin involvement is observed in approximately 5-10% of all PTLD patients and must be differentiated by other cutaneous malignancy, given the fact that organ allograft recipients have an increased risk for the development of cutaneous malignancy such as squamous and basal cell carcinoma (Beynet DP et al, 2004). The Canadian PTLD Survey Group analysed 90 cases of PTLD occurring in 4283 solid organ transplant recipients followed over a nine-year period (Allen U et al, 2001). Approximately two thirds of patients presented with disease localised to a single site, of which only a quarter were within the lymph nodes. The remaining patients had solitary lesions at extra-nodal sites including kidney, bowel, liver, mediastinum and skin. More rarely, solitary lesions were seen in the lung, tonsils and central nervous system (CNS). In particular, CNS involvement, especially in paediatric patients seems to be a risk factor for poor prognosis (Maecker B et al, 2007). In

patients presenting with multiple lesions, the lymph nodes and liver were most commonly affected. In PTLD occurring after liver transplantation abdominal findings are the most common manifestation including PTLD within liver allograft and splenic abnormalities (Wu L et al, 2001). Portal masses have also been reported presenting as lesion with mass effect and intrahepatic bile duct dilatation: they have sometimes initially been treated as abscess until the diagnosis of PTLD was made (Strouse PJ et al, 1996; Armes JE et al, 1994; Sokal EM et al, 1993). Some studies have reported rates of 50% and 30% of PTLD affecting the bowel associated with high perforation rate. So after transplantation the presence of gastrointestinal disturbance should alert the clinician to the potential diagnosis of PTLD as well as the more common complications of infection and inflammation (Starzl TE et al, 1984; Steiber AC et al, 1991). Given this myriad of nonspecific clinical signs and symptoms, often masquerading PTLD as infection or adverse drug effects or reactions, or even absence of symptoms at all, methods for early detection of PTLD in transplant recipients would be extremely valuable.

## 7. Diagnosis of PTLD

The diagnosis of PTLD should be based on histological examination of biopsy tissue. Excision biopsy is preferable and needle biopsy should only be performed where excision of affected tissue is not practicable, also because PTLD may contain large areas of necrosis. Cytological preparation are useful, particularly in the analysis of effusion (Lechapt-Zalcman E et al, 2001) and can provide adequate diagnostic material particularly if ancillary studies such as phenotypic, clonal and viral analysis are also performed. Tissue should be subjected to standard histology, examined for the presence of EBV by immunostaining or in-situ hybridization, cellular infiltrates characterised by relevant phenotypic markers and clonality estimated. Although it would be ideal to sample each tumour in cases of multicentric PTLD, this is seldom possible. Each tumour may represent a separate clone and the histological grade may be underestimated in multicentric cases. The surgeon runs also the risk, in this case, of sampling a reactive node that may contain evidence of EBV infection, while the primary lymphomatous PTLD lies elsewhere. It is also useful to consider biopsy of any lesion that responds in an atypical fashion, particularly if regression is documented in other concurrent lesions.

There is no separate staging system for PTLD and it is currently staged using the same system as non-Hodgkin Lymphoma (NHL) in the normal population. Staging of the disease should include computed tomography (CT) of the abdomen and thorax and bone marrow aspiration. Fluorodeoxyglucose positron emission tomography (FDG-PET) scanning is increasingly used as an important tool in the visualization of malignant lymphoma, especially for the detection of extranodal localization and post-treatment evaluation and has shown to be superior over conventional diagnostic techniques to differentiate between residual masses as a result of vital tumour or scar tissue. Bakker et al. (Bakker NA et al, 2006) reported a case of 12 patients with a highly avid FDG PTLD. Additional sites of extranodal localization of PTLD not visualized on CT scanning were found in 50% of all patients. (figure 1)

Additional investigations should be performed as indicated, e.g. CT or magnetic resonance scan of the cranium and spinal cord or further gastrointestinal imaging. The presence of PTLD within the graft itself may sometimes be mistaken for acute rejection and if there is

diagnostic doubt, in-situ hybridisation for EBV encoded RNA, and PCR for VDJ heavy-chain rearrangements to determine clonality may be helpful. Molecular analysis of oncogenes and tumour suppressor genes will undoubtedly play an increasingly important role in predicting behaviour even if, at present, these techniques are not widely available and few genes have been analyzed.

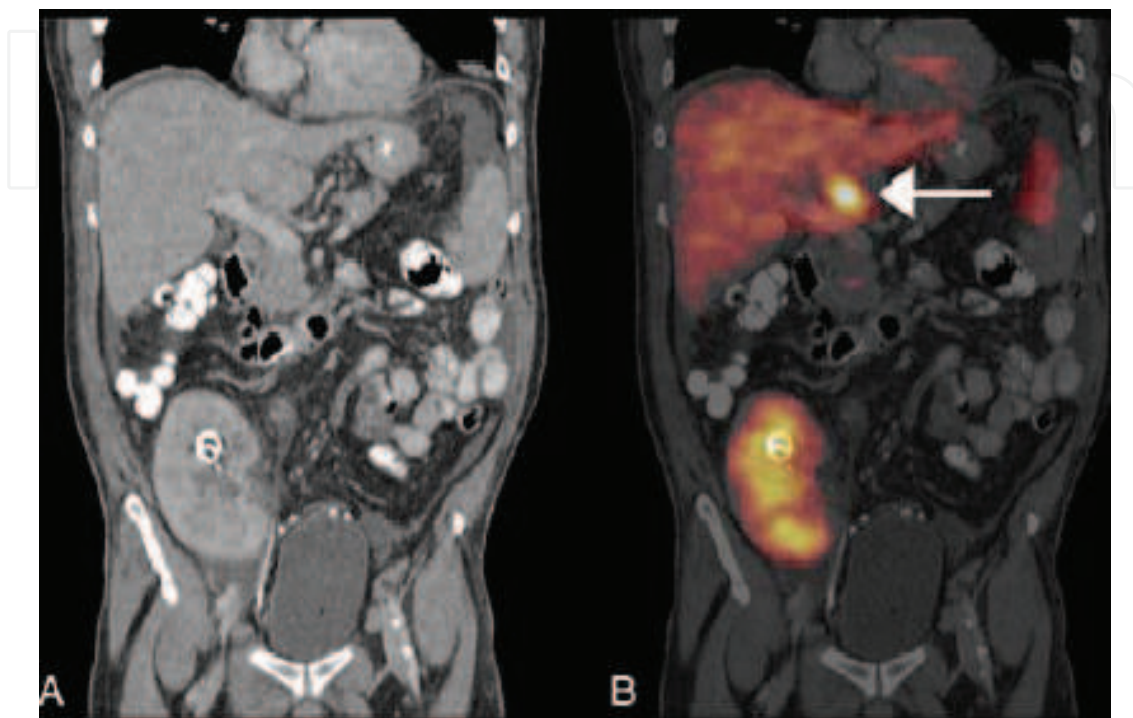


Fig. 1. Example of discordant finding. CT abdomen (A) and FDG PET fused with the same CT scan (B). Arrow indicates the histologically confirmed focal lesion with high uptake of FDG, whereas the CT scan (A) does not show any abnormalities at the site of high FDG uptake. The high uptake in the allograft, including the kidney calices and pyelum, is physiological, as is the modest uptake in liver and spleen

## 8. EBV DNA load monitoring after transplantation

Because elevation of EBV-DNA load in blood is considered to reflect aberrant EBV induced B-cell proliferation, much effort has been put in developing methods that might identify patients at risk for developing PTLD by measuring the amount of circulating EBV-DNA in the peripheral blood. More recently, pre-emptive strategies to prevent PTLD have been evaluated. Mc Diarmid et al. (McDiarmid SV et al, 1998) treated pre-emptively with intravenous ganciclovir 18 high-risk (donor positive for EBV serology, recipient negative for EBV serology) paediatric liver recipient and no one developed PTLD whereas they previously reported 10% incidence of post transplant lymphoproliferative disease (PTLD) in paediatric patients receiving first liver grafts and primarily immunosuppressed with tacrolimus. Despite the consensus that PTLD patients have a significantly higher EBV-DNA load compared with healthy EBV-seropositive donors or non-PTLD transplant recipients, it is still unclear which threshold values are predictive for PTLD. Many different threshold values have been reported, all with different sensitivity (60–100%) and specificity (71–100%) (Lee TC et al, 2005; Rowe DT et al, 2001; Tsai DE et al, 2002). Another limitation of EBV-



DNA load monitoring may be the observation that PTLD developing late after transplantation is not necessarily associated with EBV (negative staining for EBV in the tumour), and may therefore develop without a concomitant rise in EBV-DNA load. Indeed, there are studies showing EBV-negative PTLD developing late after transplantation without a rise in EBV-DNA load. These observations suggest that, although increased EBV-DNA load is generally considered to represent an increase in circulating EBV-positive tumour cells, these high EBV-DNA loads in reality may represent a separate population of proliferating B-cells that may have nothing to do with development of PTLD. Instead, these proliferating B-cells may only reflect a general state of decreased T-cell surveillance in the transplant recipient. In conclusion, because of the many variables that may influence the immune response of the individual transplant recipient, such as level of immunosuppression, time after transplantation, concomitant infections, type of organ transplanted, but also genetic factors, an exact cut-off value of EBV-DNA load critical for the development of PTLD in the individual patient cannot be defined. Therefore, rising EBV-DNA loads in the individual patient, instead of using a cut-off value, may be more appropriate to identify the individual patient at risk for the development of PTLD. It has been suggested that concomitant combined monitoring of EBV-DNA load and EBV-specific cytotoxic T lymphocytes (CTL) responses (the absence of which may be used as a marker for possible overimmunosuppression) might better identify the individual patient at risk for PTLD development. The positive predictive value of high EBV-DNA loads as a predictor for PTLD development might be improved with this method. Smets et al. (Smets F et al, 2002) showed that high EBV-DNA loads in patients who underwent primary EBV infection were indicative for PTLD development only if there was a low concomitant cellular immune response.

## 9. Clinical management

The treatment of PTLD poses a major therapeutic challenge and, although there is reasonable agreement about the overall principles of treatment no controlled studies have been undertaken and most of the recommendations result from small cohorts at single institutions.

Even if no uniform approaches to the treatment have emerged, general principles are largely shared.

- Treatment must be individualised according to clinical situation and the type of organ transplanted
- Unlike non-Hodgkin lymphoma in immunocompetent patients, PTLD can be eradicated by surgical resection
- Reduction of immunosuppression is considered the first line treatment
- Antiviral agents have showed to induce regression of disease in some cases
- Chemotherapy, traditionally considered a last resort treatment, is associated with high response rate and long progression free survival
- Rituximab has emerged as treatment of choice especially in early PTLD after failure in reduce/withdrawal immunosuppression
- Radiotherapy may be appropriate for treatment of localized PTLD together with reduction in immunosuppression

Treatment	Comments
<b>Treatments enhancing recipient CTL function</b>	
Reduction of immunosuppression	First line treatment for PTLD  More likely to induce remission in early or polymorphic PTLD
<b>Adoptive T cell therapy</b>	Risk of graft versus host disease in case of allogenic CTLs and need for dedicated facilities. Need for growing autologous CTLs
<b>Cytokine based therapies</b>	
Interferon-alpha	Several case reports of successful induction of remission with reduction of immunosuppression and interferon-a  May significantly increase the risk of organ rejection
Anti IL-6 antibodies	Promising results in phase one to two trials
<b>Antiviral agent</b>	Under development Acyclovir, ganciclovir
<b>Treatments reducing tumour mass</b>	
Surgical excision	For localized disease  Most cases not amenable to surgical resection
Local radiation	Adjunct to surgical excision  Treatment of choice for CNS PTLD
Chemotherapy	Used in aggressive disease  High mortality from sepsis and toxicity Effective in around 2/3 of selected patients
Rituximab	Promising results when combined with reduction in immunosuppression  Longer term results required to determine relapse rates

Table 1. Treatment of PTLD

9.1 Reduction of immunosuppression

Reduction of immunosuppression is the initial treatment in all patients with PTLD with the aim of increase antitumor activity. In EBV driven PTLD, this may partially restores CTL function resulting in an increase of EBV specific CTLs and elimination of virally infected lymphocytes, including those which constitute the tumour. The approach to reduce immunosuppressive drugs needs to be carefully individualised and will depend on the nature and extent of disease, the type of transplant recipient (life or no-life supporting graft) and the time from transplantation.

In general most clinicians adjust the corticosteroid dose to 10 mg of Prednisone daily in the hope to prevent allograft rejection. Steroids also are an important component of most chemotherapy regimen for PTLT and lymphoma in general.

A response to reduction in immunosuppression is usually seen within 2-4 weeks (Green M et al, 1999).

Reduction in immunosuppression leads to long term disease remission in 40-86% of paediatric patients and 25-63% of adults.

If PTLT develops within one year of the transplant up to 80% will respond to reducing in immunosuppression.

In contrast, after one year the response rate falls to 10% with 80% of mortality (Armitage JM et al, 1991).

## 9.2 The role of rituximab

PTLT is usually of B cell origin and the use of mAB to deplete B cell is a logical approach for treatment. Rituximab, a monoclonal antibody directed against CD20 antigen expressed on mature and immature B cells, results in profound and long-lasting depletion of B cell (6-8 months), together with hypogammaglobulinemia.

Rituximab is widely used in the treatment of diffuse large B cell lymphoma in immunocompetent patients with an overall survival at two years of 70% compared with 57% of patients treated with chemotherapy alone (Coiffier B et al, 2002).

Many more case reports and case series of using rituximab in PTLT are described in literature. These cases included paediatric and adult PTLT patients who underwent solid organ or bone marrow transplantations and achieved excellent results with rituximab. Most of the patients also underwent concurrent RI and some received also antiviral therapy. Many patients experienced clinical improvement within a few days after the first infusion. Most patients were treated with the standard dose of rituximab at 375 mg/m<sup>2</sup> once a week for four consecutive weeks. The majority of the case reports describe the use of rituximab in the early onset PTLT, but it might be effective also for patients with late onset PTLT. Gonzalez-Barca et al (Gonzalez-Barca E et al, 2004) reviewed data on 108 adult solid organ transplanted patients with PTLT including 36 patients who received rituximab. With a mean follow-up of 15 months, the OS of patients treated with rituximab was significantly better than for the whole group (76% vs. 21). In a multicenter, prospective phase II study, Oertel et al. (Oertel SH et al, 2005) treated 17 adult patients with PTLT with standard dose of rituximab. The mean follow-up time was 24 months. Overall response rate was obtained in 12 (71%) patients. Nine patients (53%) achieved complete remission (CR), with a mean duration of 17.8 months. Two patients relapsed, respectively 3 and 5 months after obtaining CR. The mean overall survival was 37 months with 11 (65%) patients alive at the end of the study. Adverse events were rare and of low grade. Patients whose tumour was EBV positive were significantly more likely to achieve CR than patients with tumors that were EBV negative. The largest prospective trial of using rituximab in PTLT was published by Choquet et al. (Choquet S et al, 2005). This multicenter, open label, European phase II trial, enrolled 63 patients with PTLT after solid organ transplantation who did not improve after

reduction of immunosuppression. The study included both paediatric and adult patients who were treated with standard dose of Rituximab 375 mg/m<sup>2</sup> weekly for 4 weeks. Most of the PTLD cases were of relatively late onset with only 17 patients with PTLD diagnosed <1 year after their transplantation. The overall response rate after single agent rituximab was 59% with a CR rate of 42% and a partial response rate of 17%. Stable disease was observed in 3% of patients and 38% progressed during treatment. At a median follow up of 16.3 months, median progression free survival was 6.0 months. Trappe et al. (Trappe RU et al, 2007) reported the efficacy of single agent Rituximab in eight patients (seven adults, one paediatric) with PTLD relapsed or refractory to chemotherapy after failure of reduction in immunosuppression. Complete remission was obtained in three patients and partial remission in two. Patient achieving CR either remain in CR or were successfully salvaged again with single agent Rituximab. In conclusion patients treated with rituximab benefit from the short duration of such therapy in terms of response rate and less toxic effect. However, because of the high relapse rate observed in several studies, the combination of Rituximab with cytotoxic drugs is recommended to be evaluated.

### 9.3 Antiviral agents

Because most PTLDs arise as a consequence of EBV infection, prophylactic measures should include avoiding over-immunosuppression of the recipient such as the use of anti-lymphocyte preparations, antiviral agents, EBV vaccination, in-vitro generated EBV specific CTL lines and avoiding, in EBV seronegative recipients, transplantation with an organ from an EBV positive donor. Regression has been described following high dose acyclovir. Targeting EBV by antiviral agents has been attempted also for prophylaxis of PTLD. An alternative approach, especially in high risk recipients, is to prospectively monitor the EBV viral load after transplantation and to initiate therapy when a pre-determined threshold is exceeded. One problem with this approach is that only a minority of patients with high EBV loads develops PTLD, and some patients with EBV-positive PTLD may have a low serum viral load

### 9.4 Cytokine based therapy

Agents that alter the cytokine environment of the tumour to favour remission, notably interferon- $\alpha$  (Davis CL et al, 1998) and anti-IL-6 have been tried as adjuvant along with reduction of immunosuppression, but at present there is insufficient evidence to recommend their routine use. Interferon- $\alpha$  enhances T-lymphocyte cytotoxicity and has been used as an adjunct to chemotherapy to treat B cell malignancies in non-transplanted patients and in the maintenance of remission in such patients. Swinnen et al. (Swinnen LJ et al, 2008) recently reported results of a trial for treatment of PTLD starting with a defined course of RI in all patients, escalating to interferon (IFN) alpha2b, and finally to chemotherapy, in a prospective multicenter phase II study of adult solid organ transplant recipients. Reduction in immunosuppression produced no CR, progressive disease and rejection were frequent; response to IFN was rare while chemotherapy resulted in 57% durable CR. IL-6 may play a role in the development of PTLD by promoting the growth of EBV-infected B cells and increasing tumour development in EBV-immortalised cells. Serum levels of IL-6 are raised in the majority of patients with PTLD. Anti-IL-6 mAb has been used in a phase 1-2 multi-centre clinical trial in 12 patients with PTLD that was refractory to a

reduction of immunosuppression (Haddad E et al, 2001). Five of the 12 patients showed a complete response with no residual tumour and three patients showed a decrease in tumour size, which in one case was sufficient to allow surgical removal of a previously unresectable tumour. Anti-IL-6, therefore, appears to be a promising adjunct in the treatment of PTLT but further studies are needed to fully assess its efficacy.

### 9.5 Rapamycine

Rapamycine is increasingly used as an immunosuppressive agent for solid organ transplantation. In addition to its immunosuppressive effects, it also displays anti-angiogenic and anti-tumour properties, and this make it a potentially attractive agent for patients in remission from PTLT, particularly those who develop chronic allograft rejection as a consequence of a reduction of immunosuppression. Rapamycin inhibits the growth of EBV-transformed B lymphocyte lines in-vitro by arresting cell cycle in the G1 phase (Vaysberg M et al, 2007). There are no prospective studies addressing the use of rapamycin in the treatment or prevention of PTLT.

### 9.6 Adoptive T cell therapy

Adoptive T cell therapy using EBV-specific CTL lines has generated considerable interest as a treatment for PTLT. Adoptive immunotherapy was initially advocated in allogeneic bone marrow transplantation to control PTLT that was donor cell in origin. Donor CTL would restore immune surveillance against EBV driven proliferation and control PTLT. A potential risk was graft versus host disease due to the donor cell infusion: this risk could be reduced by selecting donor EBV-specific T cell ex vivo prior to infusion. This approach has been used with success as prophylaxis and treatment of PTLT after stem cell transplantation using CTL lines derived from the donor and specific for EBV gene products even if it is limited by the time required to generate the CTLs (weeks to months) and the expense for dedicated facilities. Haque et al (Haque T et al, 2007) presented the results of a recent multicenter clinical trial using Epstein-Barr virus-specific CTL generated from EBV-seropositive blood donors to treat patients with EBV-positive PTLT on the basis of the best HLA match and specific in vitro cytotoxicity. The response rate (complete or partial) in 33 patients was 64% at 5 weeks and 52% at 6 months. Fourteen patients achieved a complete remission, 3 showed a partial response, and 16 had no response at 6 months (5 died before completing treatment). No adverse effects of CTL infusions were observed. These results showed that allogeneic CTLs are a safe and rapid therapy for PTLT, bypassing the need to grow CTLs for individual patients. After solid organ transplantation, PTLT is usually of recipient origin and recipient derived CTLs are required for effective killing of EBV infected B cells. It is possible to generate autologous EBV-specific CTLs from recipients who were EBV seropositive prior to transplantation. However, this approach is not applicable when PTLT arises in recipients who were EBV seronegative prior to transplantation. Savoldo et al (Savoldo B et al, 2006) treated 12 patients with persisting high EBV-DNA viral load with no evidence of PTLT (6 patients) or high EBV-DNA load with previous or current clinical diagnosis of PTLT (6 patients). Ten of the 12 patients had no evidence of overt PTLT following CTLs therapy, despite being categorized at high risk because of persisting of high EBV-DNA viral load. The two remaining patients both had evidence of pre-existing PTLT and both appeared to respond to CTLs infusion.



### 9.7 Chemotherapy

Conventional cytotoxic chemotherapy which has been shown to be curative for many lymphomas in non-PTLD setting, has been viewed as a treatment of last resort due to very high morbidity and mortality rates. Chemotherapy is commonly used in the treatment of PTLD when reduction in immunosuppression fails to control the disease.

Various multi-drug regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) have been used in PTLD patients (Wasson S et al, 2006; Elstrom RL et al, 2006; Trappe R et al, 2007; Taylor AL et al, 2006; Fohrer C et al, 2006; Buadi F et al, 2007; Patel H et al, 2007; Aversa SML et al, 2008)

In spite of the high response rate up to 70%, the associated toxicity is significant and includes treatment-related deaths in about 25% of patients. The high mortality of the standard chemotherapy regimens in the PTLD population might occur because of various factors including baseline pharmacologic immunosuppression, graft dysfunction, and colonization with resistant or hospital acquired infectious organisms.

Sepsis and other complication of chemotherapy have been the major problem in some centres, while others have found refractory disease to be common.

PTLDs after liver transplantation reported in literature are most of all cases report and only few studies analyze a larger group of this disease. (Table 2)

Ben-Ari et al ( Ben-Ari Z et al, 1999) reported a series of 7 patients who developed PTLD between 1988 and 1997. 2 patients with late PTLD received anthracycline based chemotherapy and actually they are alive with no recurrence of disease respectively 10 months and 24 months after the end of treatment. Another one with polyclonal tumour EBV positive, was initially treated with high dose acyclovir IV. However he progressed to monoclonality and systemic chemotherapy (CHOP) was instituted: the patient died 7 months later after one cycle of chemotherapy of septicaemia and rapidly progressive lymphoma.

Norin et al (Norin S et al, 2004) observed, in a population of 500 consecutive recipients of liver graft, 9 cases of monomorphic PTLD, one case of polymorphic PTLD and two case of unclassifiable NHL developed at a median time from transplantation of 19,5 months (1,5-148). Chemotherapy (CHOP or VACOP-B) was used in all patients mostly upfront but in one patient 4 months after diagnosis because of lack of response to reduced immunosuppression alone. Ten patients had a complete remission, one a partial remission and one a stable disease. Six patients are alive and in complete remission more than 4 years after the lymphoma diagnosis while 6 patients died because of progression of lymphoma in three, neutropenic sepsis in two and recurrence of cirrhosis in one.

Lorenzini et al (Lorenzini S et al, 2006) described a small series of 4 monomorphic PTLD. Two were early PTLD and EBV was detected in tumour tissue. The other was late PTLD and only one presented Latent membrane protein type 1 in lymphoma tissue. In all patients the immunosuppressive regimen was reduced. All patients underwent also two consecutive cycles of Rituximab and no severe adverse events were observed during the treatment period. Two patients received chemotherapy at progression but they died despite CHOP therapy. Only one patient, with monomorphic late PTLD is alive 5 years after disease onset. In this case lymphoma remission was obtained with reduction in immunosuppression and Rituximab administration.

	Number of patients who received chemotherapy/	Chemotherapy	response	Therapy related mortality
*Ben Ari et al (102)	4/7	2 CHOP 1 Vincristine 1 MACOP-B	2 CR 2 PD	None
*Norin et al. (103)	12/12	8 CHOP 1 Epi CEBOP 1 Paclitaxel 1 VACOP B 1 BFM90 course	10 CR 1 SD 1 PD	2 neutropenic sepsis
*Lorenzini et al. (104)	4/4	2 R+CHOP 2 Rituximab	1 CR 3 PD	None
*Kremers et al. (105)	11/37	11 CHOP or BACOP 5 Rituximab	na	None
*Avolio et al. (106)	5/5	1 R+CVP 1 R+CHOP 2 CHOP 1 ABVD	3 CR 2 PD	None
*Patel et al. (107)	10/17	5 CHOP 5 Rituximab	8 CR 2 PD	None

\* retrospective study  
CR: complete remission; PD: progression disease; SD: stable disease; CHOP-R cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab; MACOP B: Methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin; CEBOP: cyclophosphamide, etoposide, bleomycin, vincristine, prednisone; VACOP-B: etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin; BACOP: bleomycin, doxorubicin, cyclophosphamide, vincristine, prednisone; CVP: cyclophosphamide, vincristine, prednisone ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine.

Table 2. Chemotherapy treatment of patients with PTLD after liver transplantation

In a retrospective study by Kremers et al (Kremers WK et al, 2006), among 1206 liver transplantation recipients, 37 patients developed PTLD. Eleven received chemotherapy (CHOP-BACOP) because of stable or progressive disease despite reduction of immunosuppression. Surprisingly, survival post PTLD diagnosis was very similar both for the EBV positive and EBV negative PTLD regardless of treatment received.

Avolio et al (Avolio AW et al, 2007) treated 5 patients with PTLD after liver transplantation. Two patients with early EBV positive PTLD received three doses of R-CVP and CHOP respectively but, after an initial response, they relapsed with progression of lymphoma and rapidly died. Among the three cases of late PTLD, 2 presented a monomorphic monoclonal disease and one a Hodgkin Lymphoma. EBV was negative in one. They received soon discontinuance of immunosuppression and chemotherapy (R-CHOP-ABVD) and they are alive without evidence of disease.

In a retrospective analysis of 17 consecutive cases (6 early and 11 late disease) of PTLD associated with liver transplantation (Patel H et al, 2007), 5 patients received chemotherapy

(CHOP), 4 obtained CR and one developed progression of disease. At a median follow up of 4,25 years only 5 patients of the entire series are alive and in clinical and radiological remission.

Marino et al (Marino D et al, 2010) reported on 10 consecutive cases of PTLD after liver transplantation with seven monomorphic diseases. Chemotherapy was used in eight patients. No treatment-related mortality was observed and no patient developed graft rejection during chemotherapy. At a median follow-up period of 25 months, 6 of the 10 patients were alive and without evidence of disease.

## 10. Conclusion

The patients with PTLD can be treated with chemotherapy with an overall response rate of 77% obtaining a long term disease free survival.

In immunocompetent patients, Rituximab administration represents an important step in the treatment of non Hodgkin Lymphoma and currently immunochemotherapy is the gold standard for this kind of patients (Coiffier B et al, 2002; Pfreundschuh M et al, 2008).

However, Rituximab increases the risk of CMV and Aspergillus infections (Hirokawa M et al, 2007; Askoy S et al, 2007; Suzan F et al, 2001; Van der Velden WJ et al, 2006) both in immunocompetent and in post transplant immunosuppressed patients. Recent data also report an anti-rejection activity of Rituximab (Kaposztas Z et al, 2009; Mulley WR et al 2009).

In conclusion Rituximab represents a good option in the treatment of PTLD but there are few studies with small population, so the survival rate with the use of this antibody needs to be assessed together with chemotherapy administration in patients with PTLD.

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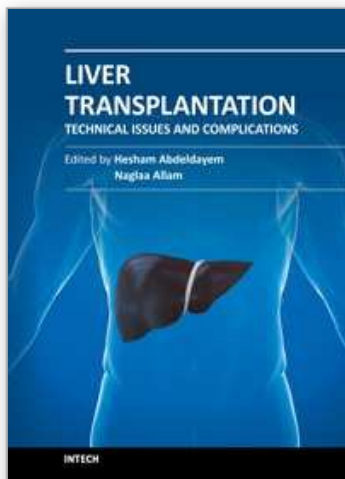
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## **Liver Transplantation - Technical Issues and Complications**

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This book covers a wide spectrum of topics including, but not limited to, the technical issues in living and deceased donor liver transplant procedures, cell and experimental liver transplantation, and the complications of liver transplantation. Some of the very important topics, such as the arterial reconstruction in living donor liver transplantation, biliary complications, and the post-transplant-lymphoproliferative disorders (PTLD), have been covered in more than one chapter.

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