DR. SHIREEN KASSAM (Orcid ID : 0000-0002-6173-3326)

Article type : Original Article

Title: A retrospective analysis of post transplant lymphoproliferative disorder following liver transplantation.

Authors: Feras Al Fararjeh[1], Shameem Mahmood[1], Phaedra Tachtatzis[1], Deborah Yallop[1], Stephen Devereux[1], Piers Patten[1], Kosh Agrawal[2], Abid Suddle[2], John O'Grady[2], Nigel Heaton[2], Robert Marcus[1], Shireen Kassam[1]

[1]Department of Haematology and [2]Department of Hepatology, King's College Hospital NHS Foundation Trust, London, UK.

Corresponding Author:

Dr Shireen Kassam

Haematological Medicine

King's College Hospital
Ground Floor, Hambledon Wing

Denmark Hill,
London SE5 9RS

020 3299 5262

Shireen.kassam@nhs.net

Running title:

PTLD following liver transplantation

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/ejh.12988

Abstract:

Objective

To evaluate response rates and survival in adults developing post-transplant lymphoproliferative disorder (PTLD) following liver transplantation

Methods

Patients were identified retrospectively and data collected through local liver and haematology electronic databases and pharmacy records.

Results

Forty-five patients were identified. The median age at first transplant and at development of PTLD was 48 and 54 years respectively, with the median time from transplant to PTLD diagnosis of 56 months. The majority of cases (76%) were monomorphic B-cell lymphomas and 36% of tumours were EBV positive. Treatment involved reduction in immune-suppression (RIS) in 30 (67%) with RIS the only treatment in 3. Ten (22%) patients were treated with rituximab alone, 13 (29%) with chemotherapy alone and 14 (31%) patients were treated with rituximab and chemotherapy. Twenty-six (58%) patients achieved a complete response (CR). At a median follow-up of 27 months the median overall survival (OS) was 50 months Response and OS were not associated with clinical factors or the use of rituximab.

Conclusion

Outcomes reported in this study are favourable and comparable to those reported previously. The addition of rituximab did not appear to have improved outcomes in this series, although a significant proportion of patients were able to avoid chemotherapy.

Key words: Rituximab, non-Hodgkin lymphoma, Rituximab

Introduction

PTLD represent a broad spectrum of lymphoid proliferations that occur after solid organ or allogeneic haematopoietic stem cell transplantation (1, 2). It is the most common malignancy complicating solid organ transplantation (excluding non-melanoma skin cancer), accounting for approximately 20% of all cancers (1, 3). The majority of cases occur in the first year of transplant and the overall incidence of PTLD following liver transplantation is reported to be 1-4% with a higher incidence seen in children (2, 4-6).

The risk of developing PTLD is variable and depends on the type of organ transplanted, the immunosuppression regimen, recipient age, time post-transplantation, ethnicity (2, 7, 8) and both patient and donor EBV status prior to transplant (9). The degree of immunosuppression post transplant has long been considered a major determinant of the development of PTLD and the degree of T-cell suppression appears to be more important than the degree of overall immunosuppression (10, 11). The risk of PTLD tends to be lower following liver transplantation compared to other solid organ transplants, presumably due to the lower levels of immune suppression required to prevent graft rejection (2). PTLD shares common features with other immunodeficiency related lymphomas such as a preferential representation of non-Hodgkin lymphoma (NHL) versus Hodgkin lymphoma, B-cell origin, involvement of extranodal and unusual sites, high grade histology, aggressive clinical behaviour and frequent association with EBV infection (12-14).

The current histological classification of PTLD is described in the World Health Organisation (WHO) classification of haematopoietic tumours and classifies PTLD into early lesions, polymorphic and monomorphic PTLD. The latter is then divided into B- and T-cell lymphomas that resemble those occurring in the immunocompetent state (15).

Treatment can be challenging with a higher reported rate of treatment-related death compared with lymphomas in the immunocompetent setting. RIS is the main stay of treatment for early and polymorphic PTLD but this is insufficient for treatment of most monomorphic subtypes which usually require treatment with combination chemotherapy (16). More recently, the monoclonal anti CD20 antibody rituximab, has been used as first line treatment of B-cell PTLDs, reserving chemotherapy for those with more high-risk features or those with an incomplete response (17, 18). More novel cellular therapies, including EBV-specific cytotoxic T-cells (CTLs), have also been investigated and are in clinical development (19).

This study from the largest liver transplant unit in the United Kingdom reports the outcome of a retrospective series of adult patients developing PTLD.

Patients and methods

Patients

This retrospective study included 45 adult patients who received a liver transplant at King's College Hospital, London, UK, between 1986 and 2014 and subsequently developed PTLD. Patients were identified through local liver and haematology electronic databases and pharmacy records. Data were collected from electronic patient records and clinical notes. Data cut-off was 31st January 2017.

Diagnosis and Staging

The histological diagnosis of lymphoma was confirmed by biopsy according to the classification in use at the time. Prior to 2008, lymphomas were in general classified into their cell of origin, i.e. B-cell or T-cell, and into low, intermediate or high-grade (20). From 2008 onwards, lymphomas diagnosed at our institution have been classified as per the WHO classification (15). EBV status of the tumour was determined by in situ hybridisation assays for EBV-encoded RNA (EBER). Some patients had EBV PCR performed on the blood. Staging investigations included either a computed tomography (CT) scan of the neck, chest abdomen and pelvis or a [^{18}F]-fluoro-2-deoxy-D-glucose positron emission tomography (^{18}F-FDG-PET)-CT and bone marrow biopsy as appropriate**.**

Treatment

The management and treatment of all patients was reviewed and agreed upon by the King's College Hospital lymphoma multidisciplinary meeting. If appropriate from the liver transplant perspective, RIS formed part of the initial treatment approach. Standard treatment at our institution for monomorphic PTLD has been anthracycline-containing combination chemotherapy regimens, most commonly 6 cycles of CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone). From 2000, a dose of rituximab, a monoclonal anti CD20 antibody, has been added to each cycle of chemotherapy for patients with B-cell lymphomas. More recently, based on phase II study data, 4 weekly doses of rituximab (375mg/m2) alone has been used as initial treatment and chemotherapy reserved for those not achieving a complete response (18).

Definitions

The primary end point was overall response rate (ORR). Secondary end points were progression-free survival (PFS) and OS. OS was measured from the date of diagnosis of PTLD to the date of last follow-up or death. PFS was determined in patients achieving a CR and was measured from the date of CR

to the date of disease relapse. Early PTLD was defined as occurring in the first 24 months post transplant and late after 24 months.

Response evaluation

Response to treatment was determined 4-6 weeks following the last cycle of chemotherapy according to standard criteria at the time by the treating physician (21). Response was assessed by CT scan in 30 (67%) patients and ^{18}F-FDG-PET /CT in 11 (24%). In addition, based on the site of disease, one patient had a colonoscopy and one a gastric endoscopy as part of disease reassessment. Four patients died prior to response assessment

Statistical analysis

Statistical analysis was performed using GraphPad PRISM® version 5 (GraphPAD Software, San Diego, CA). The Kaplan-Meier method was used to construct OS and PFS curves. A p-value less than 0.05 was considered statistically significant.

Results:

Patient characteristics

During this 28 years period, 4774 liver transplants have been carried out at King's College Hospital. However, around 25% of patients have been lost to follow-up as they have been discharged back to the care of their referring hospitals. Therefore, the incidence of PTLD in this cohort is approximately 1%. Patient characteristics of the 45 patients are shown in Table 1. Twenty-five patients (56%) were male and the median age at the time of PTLD was 54 years (range 23-73 years). The median age at first transplant was 48 years (range 15-65 years) and 10 patients had undergone a second liver transplant for rejection. The most common indication for transplant was autoimmune liver disease in 16 (36%) patients (primary sclerosing cholangitis; 8, autoimmune hepatitis; 4, primary biliary

cirrhosis; 4). The median time from first transplant to development of PTLD was 56 months (range 2-195 months) with 13 (29%) occurring in the first 2 years post transplant. The histological subtype and stage are shown in table 2. The majority of cases, 34 (77%), were monomorphic B-cell lymphomas. One patient was treated on the basis of EBV viraemia alone and therefore did not have biopsy proven PTLD. Tumour EBV status was available in 36 (81%) patients and was positive in 16 cases (44%). EBV PCR from the peripheral blood were available for 36 (81%) and 16 patients had EBV viraemia with a median viral load of 28044 copies/ml (range 58-1065004). Interestingly, 5 patients with an EBV viraemia had a tumour negative for EBV. The rate of tumour EBV positivity was not significantly different in those developing PTLD early (within 24 months of transplant) and those developing it late; 33% vs 38% respectively (p=0.8). Most patients, 29 (66%), had advanced stage disease (stage III/IV), with 13 (29%) having stage 4 disease, including 2 patients with 2 extra-nodal sites involved. Eight of 12 patients (67%) with stage 1 disease had extranodal involvement, including 4 with small bowel involvement, 2 large bowel and 1 with involvement of the liver graft. Overall, the most commonly involved extranodal sites were the liver graft in 10 (22%), followed by the bone marrow in 7 (16%) and small bowel in 6 (13%). The immunosuppression regimen at the time of PTLD diagnosis is shown in table 1.

Treatment

The initial PTLD therapy is shown in Figure 1. This included RIS in 30 patients (67%). In 3 patients with early lesions this was the only treatment received. Three patients with stage 1 disease underwent surgical resection, with 1 patient receiving rituximab following surgery. One patient with stage 1 disease received radiotherapy alone. Thirty-eight patients (84%) required systemic anti-cancer treatment. Thirty-three patients with monomorphic B-cell lymphoma received systemic treatment, which included single agent rituximab in 10 (22%) patients, combination chemotherapy in 10 (22%) and rituximab with combination chemotherapy 13 (29%). The chemotherapy regimen

was CHOP in 21 patients (47%). One patient received COP due to cardiac dysfunction and inability to received anthracycline and 1 patient was treated with single agent vincristine. One patient had monomorphic PTLD consisting of cells with plasma cell differentiation lacking CD20 expression and was treated with bortezomib, cyclophosphamide and dexamethasone. Two patients with monomorphic T-cell lymphomas were treated with CHOP and IVE (ifosphamide, etoposide and eprirubicin) respectively. The patient with a classical Hodgkin lymphoma-type PTLD was treated with AVD (doxorubicin, vinblastine and dacarbazine). One patient with a high EBV viraemia received single agent rituximab. Two patients received EBV-specific allogeneic CTLs; one patient had a monomorphic PTLD with plasmacytic differentiation and the other had a monomorphic B-cell lymphoma and also received rituximab.

Response to treatment

The overall response rate to treatment was 76% with 26 (58%) patients achieving a CR and 8 patients achieving a partial response (PR). Eleven patients (24%) had progressive disease. In univariate analysis, response was not significantly associated with age, stage, EBV status of the tumour, or timing of PTLD post transplant. Use of rituximab per se was not associated with an improved response, however, 7 of 10 patients with monomorphic B-cell lymphoma who received single agent rituximab achieved a complete response and were able to avoid the use of cytotoxic chemotherapy. Neither patient that received CTLs had a response and neither of the patients with plasma cell differentiation responded to treatment.

Progression free survival and overall survival

At a median follow-up of 27 months (range 1-273), the median OS is 50 months (Figure 2A) with a 1, 3 and 5 year survival of 68%, 55% and 48% respectively. When only lymphoma-related deaths are

taken into account, the 1, 3, and 5 years lymphoma-free survivals are 71%, 62%, and 58% respectively (Figure 2C). The median PFS for patients achieving a CR has not been reached with a 1, 3 and 5 years PFS of 100%, 90% and 83% respectively (Figure 2B). In univariate analysis, OS was not significantly associated with age, stage, EBV status of the tumour, presence of EBV viraemia, graft involvement or timing of PTLD post transplant. In addition, neither OS nor lymphoma-free survival was impacted by the use of rituximab in B-cell lymphoma (Figure 2D).

Of the 26 patients that achieved a CR, 5 (19%) subsequently relapsed. Four of 5 patients had monomorphic B-cell lymphoma and had received rituximab as part of first line treatment (3 with chemotherapy and 1 as single agent). One relapse occurred in a patient with monomorphic T-cell lymphoma. Two of five relapsed patients received single agent rituximab and achieved a second CR and are alive at the time of data cut-off. One patient was treated with rituximab plus platinum-based combination chemotherapy but did not respond and died of lymphoma. The patients with T-cell lymphoma was treated with 3 cycles of IVE chemotherapy and achieved a second CR but then subsequently relapsed again at 21 months. One patient received EBV-directed CTLs at relapsed but had progressive disease and died.

Twenty-five patients (56%) have died; 16 from lymphoma. Other causes of death include chemotherapy-related in 1 (patient with Hodgkin lymphoma receiving AVD chemotherapy), graft failure/rejection in 4, sepsis in 1, bowel perforation in 1, pneumonia in 1, general decline in 1.

DISCUSSION:

This retrospective series from the UK's largest liver transplant unit demonstrates an incidence of PTLD following liver transplant of approximately 1%, which is at the lower end of that reported in prior studies (2, 4, 6). The most common indication for transplantation in this series is autoimmune liver disease, which is in keeping with the known higher incidence of PTLD in patients transplanted for autoimmune diseases. Transplantation for autoimmune disease represents only 10-15% of all indications for liver transplantation in our unit. The higher incidence of PTLD is likely due to the more intensive immune-suppression used post-transplant and may also reflect immune-suppression prior to transplantation either for the liver disease itself or for associated inflammatory bowel disease and other autoimmune conditions (6, 22, 23). Although previously it has been reported that the majority of PTLD cases occur early post transplant, within the first 1-2 years, more recent data suggests that late onset PTLD is more common (6, 24). This is in keeping with our data in which 71% of cases occurred beyond 24 months. However, in contrast to other series in which PTLD occurring early is usually EBV positive, our series shows a similar distribution of EBV positive PTLD in the early and late groups with the caveat that there are missing data (24, 25).

Overall, the outcome for patients in our series is favourable with a median OS of 50 months and a lymphoma-free survival at 5 years of 58%. This is comparable to a recently published series of 32 cases of post liver transplant PTLD occurring over a 12 year period in which the 1, 3 and 5 year survival was 81, 74 and 60% respectively (6). In a series of 80 patients with PTLD following all solid organ transplantation the 3-year OS was 62% (24). Most studies have reported a high rate of treatment-related death in the order of 5-30%, however, there was only one treatment death in our series (16-18). The outcome for those patients achieving a CR appears favourable with a 5 year PFS of 83%. Of the 5 patients that relapsed 3 obtained a second CR.

As expected the most common histological subtype of PTLD was monomorphic B-cell lymphoma. In general, the prognosis of this subtype has improved with the introduction better supportive care (use of granulocyte stimulating factor and prophylactic antibiotics), the use of rituximab and the recognition that not all patients require cytotoxic chemotherapy. In the phase 2 PTLD-1 study, 70 patients with CD20 positive lymphoma were treated sequentially with 4 doses of weekly rituximab followed by 4 cycles of CHOP chemotherapy. The ORR to single agent rituximab was 60% with 20% CR and following CHOP chemotherapy 90% (68% CR). PFS at 3 and 5 years was 69% and 66% with a median OS of 6.6 years. Treatment-related death was 11% (17). A follow on phase 2 study stratified 152 patients with CD20 positive PTLD based on their response to 4 doses of rituximab. All patients received 4 doses of rituximab and if a CR was achieved the response was consolidated with 4 further doses. However, if there was an incomplete response or progressive disease patients went onto received 4 cycles of rituximab with CHOP chemotherapy. Twenty-five percent of patients achieved a CR with rituximab alone and therefore avoided chemotherapy. The ORR for all patients was 88% with CR in 70%. Treatment-related death occurred in 8% of patients. The median OS was 6.6 years with a 3 year OS of 70% (18). In our study, the use of rituximab did not in itself increase response rates or OS in patients with B-cell lymphoma, although these data need to be interpreted with caution as the patients treated with and without rituximab were diagnosed and treated in different decades with differing treatment approaches. For patients treated in more recent years, 7/10 patients who received single agent rituximab achieved a CR and were able to avoid the use of cytotoxic chemotherapy. This may have contributed to the overall low treatment-related death and also confirms that immune suppression-related lymphomas may not require conventional anthracycline-based chemotherapy regimens since there is the opportunity to modulate the immune system to achieve meaningful responses. Avoidance of chemotherapy is also desirable to decrease long-term sequelae such as cardiac failure and peripheral neuropathy.

In this study, we did not identify any impact of several clinical variables on response rates or OS including age, stage, early or late PTLD, EBV status and graft involvement. (6, 24, 26). This is possibly due to sample size. We included one patient in this study who was treated with single agent rituximab for EBV reactivation alone with no clinical evidence of PTLD. The role of EBV monitoring and pre-emptive treatment in adults undergoing solid organ transplantation is controversial, given the lack of consensus of a threshold EBV copy number that is sufficiently sensitive and specific to justify treatment (27). In general, our centre does not pre-emptively treat EBV reactivation.

This study provides real-world experience of the treatment of PTLD following liver transplantation. It confirms that favourable outcomes can be achieved and that intensive chemotherapy regimens may not be required to achieve meaningful responses even in histologically aggressive tumours.

Conflict of interests

None declared

REFERENCES:

1. Penn I. Cancers complicating organ transplantation. N Engl J Med. 1990;323(25):1767-9.

2. Mukthinuthalapati PK, Gotur R, Ghabril M. Incidence, risk factors and outcomes of de novo malignancies post liver transplantation. World J Hepatol. 2016;8(12):533-44.

3. Adami J, Gabel H, Lindelof B, Ekstrom K, Rydh B, Glimelius B, et al. Cancer risk following organ transplantation: a nationwide cohort study in Sweden. Br J Cancer. 2003;89(7):1221-7.

4. Jain A, Nalesnik M, Reyes J, Pokharna R, Mazariegos G, Green M, et al. Posttransplant lymphoproliferative disorders in liver transplantation: a 20-year experience. Ann Surg. 2002;236(4):429-36; discussion 36-7.

5. Hsiao CY, Lee PH, Ho CM, Wu YM, Ho MC, Hu RH. Post-transplant malignancy in liver transplantation: a single center experience. Medicine (Baltimore). 2014;93(28):e310.

6. Mumtaz K, Faisal N, Marquez M, Healey A, Lilly LB, Renner EL. Post-transplant lymphoproliferative disorder in liver recipients: Characteristics, management, and outcome from a single-centre experience with >1000 liver transplantations. Can J Gastroenterol Hepatol. 2015;29(8):417-22.

7. Smith JM, Rudser K, Gillen D, Kestenbaum B, Seliger S, Weiss N, et al. Risk of lymphoma after renal transplantation varies with time: an analysis of the United States Renal Data System. Transplantation. 2006;81(2):175-80.

8. Caillard S, Lelong C, Pessione F, Moulin B, French PWG. Post-transplant lymphoproliferative disorders occurring after renal transplantation in adults: report of 230 cases from the French Registry. Am J Transplant. 2006;6(11):2735-42.

9. Walker RC, Marshall WF, Strickler JG, Wiesner RH, Velosa JA, Habermann TM, et al. Pretransplantation assessment of the risk of lymphoproliferative disorder. Clin Infect Dis. 1995;20(5):1346-53.

10. Opelz G, Dohler B. Lymphomas after solid organ transplantation: a collaborative transplant study report. Am J Transplant. 2004;4(2):222-30.

11. Cherikh WS, Kauffman HM, McBride MA, Maghirang J, Swinnen LJ, Hanto DW. Association of the type of induction immunosuppression with posttransplant lymphoproliferative disorder, graft survival, and patient survival after primary kidney transplantation. Transplantation. 2003;76(9):1289-93.

12. Knowles DM. Immunodeficiency-associated lymphoproliferative disorders. Mod Pathol. 1999;12(2):200-17.

13. Capello D, Rossi D, Gaidano G. Post-transplant lymphoproliferative disorders: molecular basis of disease histogenesis and pathogenesis. Hematol Oncol. 2005;23(2):61-7.

14. Dharnidharka VR, Webster AC, Martinez OM, Preiksaitis JK, Leblond V, Choquet S. Post-transplant lymphoproliferative disorders. Nat Rev Dis Primers. 2016;2:15088.

15. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon: IARC press. 2008(4th Edition).

16. Choquet S, Trappe R, Leblond V, Jager U, Davi F, Oertel S. CHOP-21 for the treatment of post-transplant lymphoproliferative disorders (PTLD) following solid organ transplantation. Haematologica. 2007;92(2):273-4.

17. Trappe R, Oertel S, Leblond V, Mollee P, Sender M, Reinke P, et al. Sequential treatment with rituximab followed by CHOP chemotherapy in adult B-cell post-transplant lymphoproliferative disorder (PTLD): the prospective international multicentre phase 2 PTLD-1 trial. Lancet Oncol. 2012;13(2):196-206.

18. Trappe RU, Dierickx D, Zimmermann H, Morschhauser F, Mollee P, Zaucha JM, et al. Response to Rituximab Induction Is a Predictive Marker in B-Cell Post-Transplant Lymphoproliferative Disorder and Allows Successful Stratification Into Rituximab or R-CHOP

Consolidation in an International, Prospective, Multicenter Phase II Trial. J Clin Oncol. 2016:JCO2016693564.

19. Ricciardelli I, Blundell MP, Brewin J, Thrasher A, Pule M, Amrolia PJ. Towards gene therapy for EBV-associated posttransplant lymphoma with genetically modified EBV-specific cytotoxic T cells. Blood. 2014;124(16):2514-22.

20. National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas: summary and description of a working formulation for clinical usage. The Non-Hodgkin's Lymphoma Pathologic Classification Project. Cancer. 1982;49(10):2112-35.

21. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007;25(5):579-86.

22. Zimmermann T, Hoppe-Lotichius M, Tripkovic V, Barreiros AP, Wehler TC, Zimmermann A, et al. Liver transplanted patients with preoperative autoimmune hepatitis and immunological disorders are at increased risk for Post-Transplant Lymphoproliferative Disease (PTLD). Eur J Intern Med. 2010;21(3):208-15.

23. Watt KD, Pedersen RA, Kremers WK, Heimbach JK, Sanchez W, Gores GJ. Long-term probability of and mortality from de novo malignancy after liver transplantation. Gastroenterology. 2009;137(6):2010-7.

24. Evens AM, David KA, Helenowski I, Nelson B, Kaufman D, Kircher SM, et al. Multicenter analysis of 80 solid organ transplantation recipients with post-transplantation lymphoproliferative disease: outcomes and prognostic factors in the modern era. J Clin Oncol. 2010;28(6):1038-46.

25. Knight JS, Tsodikov A, Cibrik DM, Ross CW, Kaminski MS, Blayney DW. Lymphoma after solid organ transplantation: risk, response to therapy, and survival at a transplantation center. J Clin Oncol. 2009;27(20):3354-62.

26. Ghobrial IM, Habermann TM, Maurer MJ, Geyer SM, Ristow KM, Larson TS, et al. Prognostic analysis for survival in adult solid organ transplant recipients with post-transplantation lymphoproliferative disorders. J Clin Oncol. 2005;23(30):7574-82.

27. Dierickx D, Tousseyn T, Gheysens O. How I treat posttransplant lymphoproliferative disorders. Blood. 2015;126(20):2274-83.

Table 1. Patient characteristics	**n=45 (%)**
Sex; male	25 (56)
Median age at 1st transplant, years	48 (15-65)
Median age at PTLD diagnosis, years	54 (23-73)
Median time to develop PTLD, months	56 (2-195)
Indications for liver transplant:	
Primary sclerosing cholangitis	8 (18)
Cirrhosis from chronic viral hepatitis	8 (18)
Cryptogenic cirrhosis	6 (13)
Alcoholic liver disease	5
Primary biliary cirrhosis	4
Autoimmune hepatitis	4
Hepatocellular carcinoma	4
Cirrhosis (NASH)	1
Acute liver failure (seronegative)	2
Acute liver failure- hepatitis A	1
Extrabiliary atresia	1
Acute liver failure Paracetamol overdose	1
Second transplant for rejection	10 (22)
Immune-suppression	
One drug	9 (20)
Two drugs	29 (64)
Three drugs	7 (16)
Tacrolimus	36 (80)
Cyclosporine	8 (18)
Prednisolone	32 (71)
Mycophenolate	3 (7)
Azathioprine	7 (16)

Table 2. Histological subtype and stage	**n=44 (%)**
Early lesions	3 (7)
Plasmacytic hyperplasia	2
Infectious mononucleosis-like	1
Polymorphic PTLD	4 (9)
Monomorphic B-cell PTLD	34 (77)
High-grade B-cell lymphoma	18 (41)
Diffuse large B-Cell Lymphoma	11 (25)
Burkitt lymphoma	3 (7)
Plasma cell myeloma	2 (5)
Plasmacytoma-like lesion	0
Monomorphic T-cell neoplasm	2 (5%)
Peripheral T-cell lymphoma, NOS	1
Hepatosplenic T-cell lymphoma	1
Classical Hodgkin lymphoma-type PTLD	1 (2%)
Tumour EBV status	
Positive	16 (36%)
Negative	20 (44%)
Unknown	8 (18%)
Stage at diagnosis	
Stage I+II	15 (34%)
Stage III+IV	29 (66%)

Legends

Figure 1: Treatment of all 45 patients; chemo; chemotherapy, RIS; reduction of immune suppression, R; rituximab, CTLs; cytotoxic T-cells

Figure 2: Kaplain-Meier curve of overall survival (A), PFS (B) and lymphoma-free survival (C), OS based on use of rituximab in B-cell lymphoma (D)