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Reduction of Immunosuppression as Initial Therapy for Post-Transplantation Lymphoproliferative Disorder

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Abstract

Reduction of immunosuppression (RI) is commonly used to treat post-transplant lymphoproliferative disorder (PTLD) in solid organ transplant recipients. We investigated the efficacy, safety and predictors of response to RI in adult patients with PTLD. 67 patients were managed with RI alone and 30 patients were treated with surgical excision followed by adjuvant RI. The response rate to RI alone was 45% (complete response - 37%, partial response - 8%). The relapse rate in complete responders was 17%. Adjuvant RI resulted in a 27% relapse rate. The acute rejection rate following RI-containing strategies was 32% and a second transplant was feasible without relapse of PTLD. The median survival was 44 months in patients treated with RI alone and 9.5 months in patients who remained on full immunosuppression (p=0.07). Bulky disease, advanced stage and older age predicted lack of response to RI. Survival analysis demonstrated predictors of poor outcome - age, dyspnea, B symptoms, LDH level, hepatitis C, bone marrow and liver involvement. Patients with none or 1 of these factors had a 3-year overall survival of 100% and 79% respectively. These findings support the use of RI alone in low-risk PTLD and suggest factors that predict response and survival.

Introduction

Post-transplantation lymphoproliferative disorder (PTLD) is a heterogeneous group of lymphoid proliferations that arise in patients following solid organ or hematopoietic stem-cell transplantation(1,2). These neoplasms are associated with activation of Epstein-Barr virus (EBV) in 70–90% of cases(3) and are the result of pharmacologic immunosuppression, which permits B-cell proliferation in the absence of appropriate T-cell regulation(4). Therefore, reduction of immunosuppression (RI) is often the first line of therapy for this disorder. RI is a powerful therapy for PTLD, as it allows recovery of the physiologic immune surveillance of EBV-transformed cells(5). In some patients, it is curative and abrogates the need for specific anti-neoplastic therapies (6–11).

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Disclosure

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Previous attempts to define the efficacy and safety of RI for PTLD remain of limited value due to small numbers of patients(12–18). Complete response rates following RI are reported between 0–74%; this wide range likely reflects heterogeneity of patient populations and the non-standardized management of RI. Retrospective studies reveal that in many centers the proportion of patients who are managed with RI alone is low and often chemotherapy and/or rituximab are administered up front(12,15,19–21). In this report, we describe the response rates to RI when used alone as initial therapy for PTLD and determine predictors of response and survival.

Methods

Patients

Between August 1988 and June 2008, 162 adult solid organ recipients were diagnosed with PTLD at the University of Pennsylvania. Staging procedures included CT scans of the chest, abdomen and pelvis; additional modalities (MRI, endoscopies) were used to investigate specific symptoms or imaging findings. Imaging of the brain and cytological examination of CSF were performed when neurologic signs or symptoms were present. A bone marrow biopsy was reserved for patients with abnormal blood counts or disseminated disease. RI included discontinuation of mycophenolate-mofetil or azathioprine in most cases and reduction of the dose of calcineurin inhibitors (CNI) and steroids (when applicable), usually by targeting a lower blood level. Lung and heart recipients on tacrolimus were targeted to reach a blood level of 4–8 ng/ml (normally 8–12) if diagnosed within the first year or 4–6 ng/ml if diagnosed later (normally 6–8). In liver and kidney recipients tacrolimus target levels were 2–3 and 3–5 respectively. Similar rules were used for patients on cyclosporine. Close monitoring was used to adjust doses according to blood levels, PTLD response, organ function and signs of rejection. We categorized patients into “complete withdrawal” when all immunosuppressive drugs were withdrawn as opposed to “partial withdrawal”. Patients who remained on low dose steroids were still considered “complete withdrawal”.

We obtained data on clinical and pathologic characteristics, anti-neoplastic therapies and tumor responses. The WHO classification of hematopoietic tumors was used for histologic classification of PTLD(2). EBV positivity was defined as either a positive in-situ hybridization for EBV-encoded RNA (EBER) or a positive immunohistochemical stain for the Latent Membrane Protein (LMP). A negative LMP stain without an accompanying EBER stain was considered non-diagnostic(2). Tumor responses were graded according to the Response Evaluation Criteria In Solid Tumors (RECIST). Failure of RI was defined as either PTLD-related death, progression of disease, or initiation of second-line therapy. Finally, we collected information on outcome of the allograft, second transplantation following graft loss, and overall survival. We focused on first-line therapy in order to isolate the response to RI alone, which was defined as the intent-to-treat using modulation of the immunosuppressive regimen with no further intervention until progression or lack of response. Data were analyzed separately for patients who were managed with RI alone (n=67), treated with complete surgical excision of their tumor followed by RI (n=30) or managed with other 1^{st}-line modalities with or without RI (n=51). The Institutional Review Board of the University of Pennsylvania approved the study.

Statistical Analysis

Patient characteristics were compared with the *t* or χ^2 test as appropriate. Survival curves were estimated by the Kaplan-Meier method and comparisons were determined by the logrank test. The Cox proportional hazards model was used for univariate analysis of survival and logistic regression modeling was used to analyze predictors of response. Following the identification of significant predictors of response by univariate analysis, a

step-wise multivariable logistic regression model was used to select variables with independent predictive significance. Hazard ratios (HRs) and odds ratios (ORs) were calculated with 95% confidence intervals (95% CI). All statistical tests were two-sided, and P values less than 0.05 were considered significant. The analysis was conducted in SAS Release 9.1.3 (SAS Institute, Cary, NC).

Results

Patients

Of 162 adult patients diagnosed with PTLD, patients who were diagnosed at autopsy (n=9) were excluded and patients with missing response data (n=5) were only included in the survival analysis. The median number of annual PTLD diagnoses was 7 (range 2–12). Of 148 evaluable patients, 67 patients were treated with RI alone as initial therapy ("RI alone" group). We did not exclude patients who died quickly after initiation of therapy or patients who were deemed ineligible for any other line of therapy, in order to capture the variability in patient characteristics within this group and prevent a bias towards healthier patients.

Thirty patients were treated with surgical excision of a localized PTLD lesion, followed by RI ("adjuvant RI" group). These patients had an isolated skin lesion (n=15), gastrointestinal lesion (n=3) or graft PTLD (n=12). These patients were in remission following surgical excision and RI was instituted as adjuvant therapy.

Patient characteristics and clinical presentation

Table 1 displays the characteristics of patients categorized according to their first line therapy – RI alone, adjuvant RI and other modalities. RI alone was used across organ types, disease stages and in early (<1 year from transplant) and late-occurring PTLD. Complete surgical excision followed by adjuvant RI was more commonly done in kidney transplant recipients and less often in liver recipients.

There were no significant differences in organ involvement, most clinical symptoms and lab abnormalities (Table 1 and Supplementary Table 1). Patients presenting with abnormal renal function were more prevalent in the adjuvant RI group, reflecting the high proportion of kidney recipients and patients with graft PTLD in that group.

The RI groups were compared with 51 patients that were treated up front with other modalities, (Table 1). Significant baseline imbalance was found in PTLD histologic subtypes; monomorphic PTLD was diagnosed in 42/67 (63%) patients treated with RI alone (diffuse large B-cell lymphoma-like, n=34; Hodgkin lymphoma-like, n=2; plasmacytoma-like, n=4; Burkitt-like, n=2) compared to only 20/51 (39%) patients treated with other first-line therapies (DLBCL-like, n=16; plasmacytoma-like, n=2; Burkitt-like, n=1; T-cell PTLD, n=1), implying a selection of patients with monomorphic PTLD for treatment with RI alone (p=0.011). Only one patient with CNS involvement was treated with RI alone while the majority of these patients were treated with rituximab, chemotherapy and/or intrathecal chemotherapy (p=0.041). We found no significant differences in organ type, EBV positivity or CD20 expression between the groups.

In patients treated with RI alone, 17/62 patients (27%) underwent full withdrawal of immunosuppression as initial therapy: 9 kidney, 7 liver and 1 kidney/pancreas recipients. 43/62 (69%) underwent partial withdrawal: 14 kidney, 7 liver, 9 heart, 12 lung, 1 kidney/pancreas (p=0.001 for organ distribution). Two liver recipients (3%) were switched from their regimen to sirolimus. Data was not available for 5 patients. In patients treated with surgery and adjuvant RI, full withdrawal was done prior to graft removal and all other patients underwent partial withdrawal shortly after surgery.

Response to reduction of immunosuppression

Sufficient data were available to grade the responses of 62/67 patients treated with RI alone (Table 2). The overall response rate (CR + PR) was 45% and an additional 18% experienced stable disease. Among 67 patients treated with RI alone, 40 patients (60%) required second-line therapy, which included rituximab (40%), cytotoxic chemotherapy (39%) & radiotherapy (15%), either alone or in combination. Only 4 relapsed/refractory patients (6%) never received 2nd-line therapy. The median time to failure (TTF) of RI in the RI alone group was 45 days (range 1–2573) in non-responders. Among patients who had a complete response, only 4 patients (17%) relapsed and required additional therapy.

The outcome of patients treated with surgery and adjuvant RI was favorable and only 8/30 patients (27%) relapsed at a median of 5 months (range 1–86).

Allograft outcome

Table 3 displays the proportion of patients who experienced an acute rejection episode following RI, and Figure S1 displays the organ-specific outcome in the RI alone group. The acute rejection rate was 40% in patients treated with RI alone, 25% in patients treated with adjuvant RI (excluding graft removals) and 45% in patients who received rituximab with RI. Concurrent cytotoxic chemotherapy and RI resulted in a low (17%) rate of acute rejection. Five kidney recipients and one lung recipient underwent a second transplantation more than one year after resolution of their PTLD and did not experience a relapse. The degree of RI (complete vs. partial) did not predict rejection (OR 1.51; 95% CI [0.43, 5.31], P=0.52).

Survival

Kaplan-Meier estimates of survival for RI alone and adjuvant RI are presented in Figure 1. The median follow-up was 64 months. The median survival for patients treated with RI alone was 44 months (3-year OS, 55%) and the median survival for patients treated with adjuvant RI was not reached (3-year OS, 65%). For comparison, we plotted the survival of patients that were maintained on full immunosuppression throughout the treatment (“No RI” group, n=23). These patients were treated with rituximab, chemotherapy or both and did not undergo RI due to concurrent rejection (n=12), previous rejection episodes (n=4) or complex presentation with infections and/or multi-organ failure (n=7). The characteristics of these patients placed them at high risk, partially explaining their poor outcome in comparison with the RI alone group (median survival 9.5 months; 3-year OS, 34%; p=0.07).

Predictors of survival and response to RI

We evaluated multiple variables for prediction of survival and response to RI using the Cox proportional hazards model and logistic regression, respectively (Tables 4–5 and Figure 2). Early disease stage at presentation predicted favorable response to RI alone. Patients with isolated graft PTLD were considered stage I. Early stage did not only predict response to RI but to any 1st-line therapy, when analyzed on 153 patients who had sufficient data (OR 0.32; 95% CI [0.15, 0.68], p=0.003). An alternative classification of tumor spread (single vs. multiple sites), suggested previously (22), did not predict response or survival better than the Ann Arbor classification. Older age was a significant predictor of poor response to RI alone (OR 0.95 per year; 95% CI [0.92, 0.99], p=0.006), and responses were rare in patients older than 65 years (Figure 2A). Anorexia at diagnosis and bulky disease (greater than 7 cm at diagnosis), were significant predictors of poor response (ORs 0.27 and 0.103 respectively). A history of multiple allografts was associated with a better response to RI. Although most of the patients who had previous allografts represented kidney recipients, response to RI was not limited to one organ type. Responses were slightly more common among kidney recipients but recipients of other organs demonstrated good responses as well (p=0.35 for

kidney vs. non-kidney; Figure 2A). Non-significant differences in response to RI were demonstrated between major histologic subtypes, EBV status and late vs. early PTLD. The response rates among patients with uncommon histologic subtypes were 3/4 for plasmacytoma (all 3 achieved CR), 0/2 for Hodgkin-like PTLD and 1/2 for Burkitt-like lesions (PR in one responder).

After identifying variables that predicted response in univariate analysis, we applied a stepwise logistic regression model (Table 4). Independent predictors for response to RI were younger age (OR 0.94 per year), early stage (OR 0.58) and non-bulky disease (OR 0.09). Only 1/10 patients with bulky disease had a response (CR) to RI alone. Curiously, bulky disease did not predict overall survival, implying that these patients can be salvaged with 2^{nd}-line therapy.

We combined the three most significant predictors for lack of response to RI (stage, bulky disease and age over 50) into a single variable (Figure 2B). As expected, the combined variable predicted response very well (OR 0.223, p=0.001). Response rates to RI alone were 77%, 54% and 15% in patients with 0, 1 and 2–3 adverse factors respectively.

Survival analysis was performed in 67 patients managed with RI alone (Table 5). Significant predictors of poor survival were age, B symptoms, weight loss, dyspnea, hepatitis C, bone marrow and liver involvement as well as very high LDH (greater than 2.5 × ULN). The extent of increase in serum LDH levels had a very strong correlation with survival; the median survival for patients with LDH>2.5 × ULN was shorter than 2 months.

Seven risk factors that were identified as significant prognostic factors in our survival analysis were used to stratify patients for subgroup analysis (Figure 3). The 3-year OS estimates were 100%, 79%, 32% and 7.5% for patients with 0,1,2 and greater than 2 risk factors respectively (p<0.0001 in a log-rank test across strata).

Discussion

PTLD is a major cause of morbidity and mortality after solid organ transplantation. Despite advances in immunosuppression, the risk of PTLD remains significant, affecting 1–30% of transplant recipients(23–27). In this study we aimed to determine the outcome of the common initial step in the management of PTLD – withdrawal of immunosuppression. It follows common wisdom established more than 20 years ago(5): if PTLD is caused by the unchecked proliferation of EBV-transformed lymphocytes under immunosuppressive therapy, then withdrawal of immunosuppression will allow the anti-tumor effects of the immune system to recover, resulting in tumor regression.

Our study demonstrates a response rate of 45% in patients selected for treatment with RI alone, with the majority being complete responses. Only 4 relapsed/refractory patients never received 2^{nd}-line therapy, illustrating that most patients have the potential for second-line salvage if they fail RI.

Our second cohort included 30 patients who underwent surgical excision of a skin lesion, gastrointestinal mass or a graft containing PTLD, rendering them free of disease prior to adjuvant RI, intended to prevent relapse. We think of lymphoid proliferative disorders as systemic diseases and normally favor systemic therapy. Several reports have utilized surgery in PTLD(28–32), and here we describe a large group of patients, in which surgical treatment followed by RI resulted in successful control of the disease and most often permanent cure (only 27% relapsed). We did not identify a sufficient number of patients who underwent surgery *without* adjuvant RI and whether RI was necessary is a question that cannot be answered by this study.

The safety of RI has been a major concern. We demonstrated a 32% acute rejection rate with RI-containing regimens. Some of these patients recovered and others underwent a second transplantation following resolution of their PTLD (Figure S1). Keeping in mind that cytotoxic chemotherapy agents are very effective immunosuppressants, 2nd-line therapy after failure of RI can salvage an acute rejection episode. If allograft rejection becomes irreversible, a second transplant is a valid option, as demonstrated in our study and others(33, 34). Interestingly, the extent of RI failed to predict rejection, but RI strategies were unbalanced across organs and firm conclusions cannot be drawn.

Should we attempt RI alone in all patients presenting with PTLD? This study provides significant insight. First, some presumed risk factors — such as EBV negativity or monomorphic PTLD — did not show association with response. As opposed to previously published work, our study included multiple allograft types and a significant number of patients with EBV-negative disease (30% of the RI alone cohort), allowing us to demonstrate that RI can be effective in EBV-negative PTLD(35) and across all histologic subtypes and allograft types, including “high-risk” organs such as heart and lung. Second, lack of response is predictable. In the current study, we identified bulky disease, advanced stage and older age as adverse factors that predict failure to respond. Patients who lacked these factors had a 77% chance of response to RI alone. The validity of these conclusions is limited by the retrospective nature of our study and the lack of data availability for some of the important variables. Prospective studies are needed to clarify the role of previously reported biomarkers of response, such as quantitative PCR for EBV(36) and analysis of EBV-specific cytotoxic T-lymphocytes(37).

Finally, our survival analysis identified several strong predictors of poor survival, which generally reconcile with known risk factors in lymphoid malignancies (age, high LDH, B symptoms, BM involvement). These findings partially overlap previous PTLD studies, which identified age, BM and CNS involvement, LDH, performance status, and high-risk histology (Burkitt-like, T-cell) as important prognostic factors(22,32,38–41). EBV status, stage and late PTLD have been identified by some studies (22,40) but not by others (38,42), which illustrates the heterogeneity in study design, size and population (pediatric vs. adult, organ-focused vs. mixed). Our study focused on adult patients treated with RI alone and had a baseline imbalance towards monomorphic PTLD and lack of CNS involvement. Our survival analysis may therefore not apply to all PTLD patients.

Approximately 35% of patients in this study were diagnosed before the availability of rituximab, which can be used either alone or in combination with chemotherapy resulting in response rates of 50–80%(9,19,43–45). Rituximab can spare patients the risks of cytotoxic chemotherapy, but still has serious side effects, mainly infusion reactions, immune suppression and other idiosyncratic reactions(46). A recent retrospective report demonstrated favorable outcome and 3-year OS of 73% with the use of rituximab early in therapy, but all patients in that series also underwent RI initially(19). The relative contributions of RI and rituximab to the high response rate in that study are unknown. Similarly, other reports on rituximab for PTLD have focused on 2nd-line therapy(8,44,45,47). Considering the poor survival that was demonstrated in our study for patients who never underwent RI, including patients who received rituximab (Figure 1), our study underscores the importance of RI either alone or in conjunction with rituximab. Notably, our survival analysis failed to demonstrate a difference in survival between patients treated with RI alone before and after the year 2000 (p=0.91). A similar analysis performed on our entire patient cohort (n=153) also showed a non-significant difference (p=0.39), implying that the introduction of rituximab may not have resulted in a significant improvement in outcome.

Our survival analysis demonstrated two subgroups of low-risk patients, in which treatment with RI alone resulted in 3-year overall survival rates of 100% and 79%, respectively. These outcomes are similar or better compared to the recent report about rituximab(19), allowing us to hypothesize that RI alone may be sufficient in low-risk patients. It is also notable that rituximab did not seem to protect against rejection (Table 3).

Our study was not powered to differentiate between RI strategies. Complete and partial withdrawals of immunosuppression resulted in similar rates of response and rejection and in similar survival hazards, but were used in different allograft types and possibly different clinical scenarios, making it difficult to draw any conclusions on a better strategy. More specific information about RI strategies and organ-specific rates of rejection has been published(48,49).

Our observations support initial therapy with RI and close monitoring in low-risk patients. Patients who have an initial response can often be observed with frequent imaging and fine-tuning of the immunosuppressive regimen. With this strategy, many patients avoided cytotoxic chemotherapy and the associated risk of complications. Conventional chemotherapy often requires dose reductions due to underlying organ dysfunction and is associated with a poor outcome; patients in our study who required chemotherapy at any stage of their treatment had a median survival of 19 months.

Certain limitations of this study should be acknowledged. The retrospective observational nature of this study is prone to confounding and may lead to a bias in our estimates of the effects of RI and the predictors of these effects. Sample size limitations may result in failure to detect significant predictors of response or survival. In addition, our conclusions may not apply to the pediatric population, which has special characteristics and a higher incidence of primary EBV infection. Our cohort did not include a sufficient number of patients with CNS involvement or rare subtypes of PTLD such as T-cell or Hodgkin-like disease. Our conclusions may not be applicable to such patients.

To summarize, in our retrospective analysis, RI alone as initial therapy for PTLD has a high response rate and can lead to a favorable outcome. Relapse is uncommon in patients who experience a complete response to RI. Rejection is common but manageable by further adjustment of immunosuppressive therapy, second-line therapy including cytotoxic chemotherapy and in some cases a second transplant. RI can also be used efficiently and safely for patients in the adjuvant setting following resection of PTLD lesions. Older age, bulky disease and advanced stage (particularly stage IV) are associated with poor response to RI. Low-risk patients should be considered for treatment with RI alone and can expect a favorable outcome.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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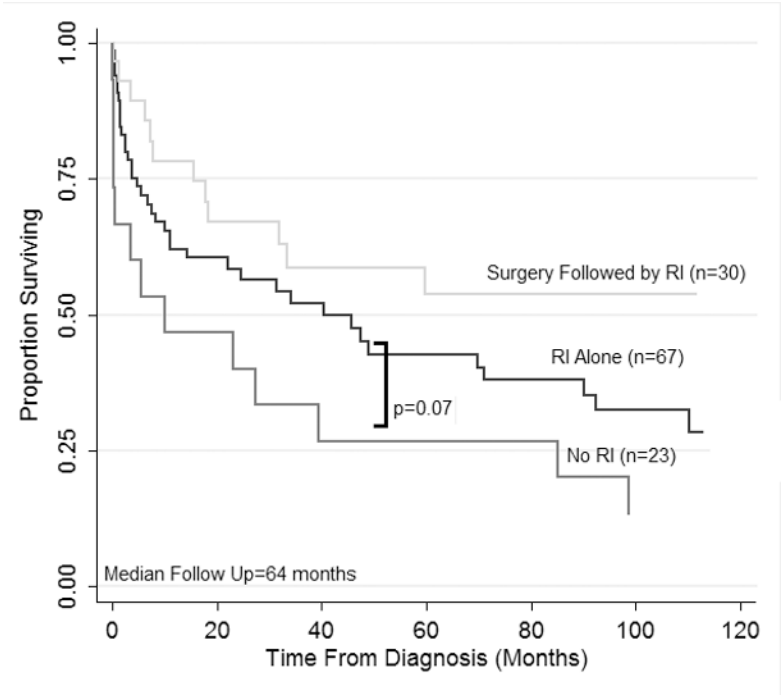

Figure 1.

Overall survival of patients with PTLD who were treated with reduction of immunosuppression (RI) alone as initial therapy (n=67), complete surgical excision of a PTLD lesion, followed by adjuvant RI (n=30), and no RI throughout treatment (n=23). Survival estimates are plotted using the Kaplan-Meier method. P=0.07 for RI alone versus No RI represents a logrank test.

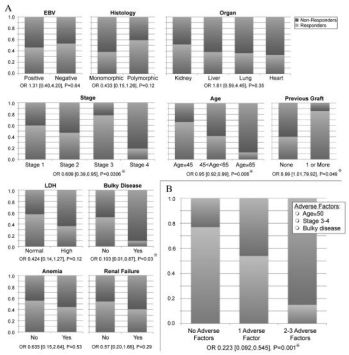

Figure 2.

Proportions of responding (Complete Response + Partial Response) and non-responding (Stable Disease + Progressive Disease) patients with PTLD following treatment with RI alone analyzed according to clinical and pathologic characteristics. Odds ratios indicate the difference in likelihood of response between subgroups and P-values indicate significance level in a logistic regression model. * P<0.05. **A.** Representative variables from Table 4. **B.** Prediction of response to RI using a summary of 3 independent adverse factors: Age≥50, advanced stage (3–4 vs. 1–2) & bulky disease (mass>7cm).

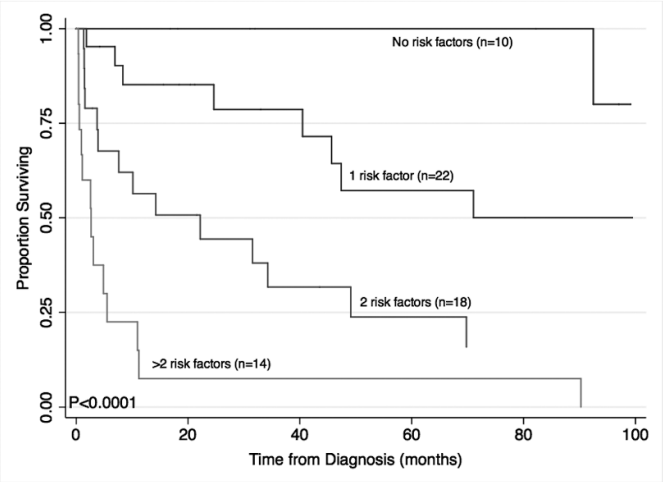

Figure 3.

Overall survival of patients with PTLD who were treated with reduction of immunosuppression (RI) alone as initial therapy stratified using a survival model that includes 7 prognostic factors: Age≥50, serum LDH>2.5×ULN, hepatitis C, liver involvement, bone marrow involvement, B symptoms, dyspnea at presentation. Survival estimates are plotted using the Kaplan-Meier method. P-values represent a logrank test across strata. Total n=64 patients with complete data.

Table 1

Patient characteristics and clinical presentation

	RI alone as initial therapy	Surgery followed by adjuvant RI	Other first-line therapies* with or without RI
Number of patients	**67**	**30**	**51**
Gender:			
Male	48 (72%)	18 (60%)	33 (65%)
Female	19 (28%)	12 (40%)	18 (35%)
Allograft type:		★	
Heart	9 (13%)	5 (17%)	10 (20%)
Lung	13 (19%)	5 (17%)	9 (17%)
Kidney	27 (40%)	15 (50%)	17 (33%)
Kidney+Pancreas	2 (3%)	3 (10%)	4 (8%)
Liver	16 (24%)	1 (3%)	10 (20%)
Pancreas	0	1 (3%)	0
Liver+Kidney	0	0	1 (2%)
Mean age at transplant (years)	45.6	41	45.6
Mean age at PTLD diagnosis (years)	50.7	46.2	51.5
Median time from transplant to PTLD (range)	871 days (56–8402)	825 days (9–6166)	963 days (6–6771)
Immunosuppressive regimen at diagnosis			
CSA+MMF	7 (11%)	0	5 (10%)
TAC+MMF	12 (19%)	5 (19%)	9 (18%)
CSA+AZA	22 (35%)	16 (59%)	16 (33%)
TAC+AZA	5 (8%)	1 (4%)	5 (10%)
CSA alone	6 (10%)	1 (4%)	8 (16%)
TAC alone	9 (14%)	1 (4%)	5 (10%)
AZA alone	2 (3%)	3 (11%)	1 (2%)
Unknown	4	3	2
Steroids at diagnosis			
Yes	56 (88%)	26 (93%)	42 (86%)
No	8 (12%)	2 (7%)	7 (14%)
Unknown	3	2	2
Hep. B – Yes	5 (11%)	0	2 (7%)
No	40 (89%)	14 (100%)	26 (93%)
Unknown	22	16	23
Hep. C – Yes	4 (11%)	1 (8%)	4 (20%)
No	33 (89%)	11 (92%)	16 (80%)

	RI alone as initial therapy	Surgery followed by adjuvant RI	Other first-line therapies* with or without RI
Unknown	30	18	31
Stage		★	
I/II	34 (52%)	30 (100%)	25 (52%)
III/IV	32 (48%)	0 (0%)	23 (48%)
Unknown	1	0	3
		★	
Single site	18 (27%)	30 (100%)	19 (40%)
Multiple sites	48 (73%)	0 (0%)	29 (60%)
Unknown	1	0	3
Previous grafts:			
1	60 (90%)	28 (93%)	47 (92%)
>1	7 (10%)	2 (7%)	4 (8%)
Previous rejection episodes – Yes	31 (52%)	11 (41%)	24 (57%)
No	29 (48%)	16 (59%)	18 (43%)
Unknown	7	3	9
B symptoms ¶ – Yes	40 (61%)	16 (57%)	31 (65%)
No	26 (39%)	12 (43%)	17 (35%)
Unknown	1	2	3
Weight loss –		★	
Yes	29 (43%)	6 (21%)	17 (35%)
No	38 (57%)	22 (79%)	31 (65%)
Unknown	0	2	3
Fever – Yes	23 (34%)	14 (50%)	20 (42%)
No	44 (66%)	14 (50%)	28 (58%)
Unknown		2	3
Night sweats- Yes	14 (21%)	5 (18%)	8 (17%)
No	53 (79%)	23 (82%)	40 (83%)
Unknown	0	2	3
Bulky disease ¶ -		★	
Yes	10 (15%)	0 (0%)	7 (15%)
No	57 (85%)	30 (100%)	40 (85%)
Unknown	0	0	4
Extranodal disease – Yes			
No	48 (73%)	27 (90%)	39 (83%)
Unknown	18 (27%)	3 (10%)	8 (17%)
	1	0	4

	RI alone as initial therapy	Surgery followed by adjuvant RI	Other first-line therapies* with or without RI
Involvement of the graft –			
Yes	16 (24%)	12 (40%)	18 (38%)
No	51 (76%)	18 (60%)	29 (62%)
Unknown	0	0	4
CNS involvement –			★
Primary	0	0	3 (6%)
Secondary	1 (2%)	0	3 (6%)
None	65 (98%)	30 (100%)	44 (88%)
unknown	1	0	1
BM involvement –			
Yes	5 (15%)	0	2 (9%)
No	28 (85%)	9 (100%)	21 (91%)
Unknown	34	21	28
Elevated Creatinine –		★	
Yes	41 (63%)	26 (93%)	34 (74%)
No	24 (37%)	2 (7%)	12 (26%)
Unknown	2	2	5
Elevated LDH – Yes	40 (65%)	15 (75%)	29 (74%)
No	22 (35%)	5 (25%)	10 (26%)
Unknown	5	10	12
Histology[Δ]:			★
Polymorphic	25 (37%)	13 (43%)	31 (61%)
Monomorphic	42 (63%)	17 (57%)	20 (39%)
Mono. Subtypes:			
DLBCL	34 (51%)	12 (40%)	16 (31%)
Plasmacytoma-like	4 (6%)	2 (7%)	2 (4%)
Hodgkin-like	2 (3%)	0	0
Burkitt-like	2 (3%)	0	1 (2%)
T-cell	0	0	1 (2%)
NOS	0	3 (10%)	0
EBV positivity[~] **- Yes**	42 (70%)	16 (80%)	28 (67%)
No	18 (30%)	4 (20%)	14 (33%)
Unknown	7	10	10
CD20 expression – Yes			
No	46 (79%)	10 (67%)	24 (71%)
Unknown	12 (21%)	5 (33%)	10 (29%)

	RI alone as initial therapy	Surgery followed by adjuvant RI	Other first-line therapies* with or without RI
	9	15	17

★P<0.05 compared to RI alone.

*Other therapies include surgery, radiotherapy, rituximab and cytotoxic chemotherapy.

¶B symptoms include weight loss, night sweats and fever. Bulky disease defined as a greater than 7cm mass or lymph node.

ΔThe WHO classification of hematopoietic tumors was used for classification of PTLD(2).

~EBV positivity was defined as either a positive EBER in-situ hybridization or positive LMP stain. A negative LMP stain without an accompanying EBER stain was considered non-diagnostic (2).

Table 2

Response rates in patients treated with RI alone

	RI Alone as Initial Therapy
Overall Response	28/62 (45%)
Complete Response	23/62 (37%)
Partial Response	5/62 (8%)
Stable Disease	11/62 (18%)
Progressive Disease	23/62 (37%)
Unknown	5

Grading of response was performed using the Response Evaluation Criteria in Solid Tumors (RECIST).

Table 3

Acute allograft rejection in patients treated with reduction of immunosuppression (RI) alone and in combination

Regimen	Incidence of Acute Graft Rejection
RI alone	20/50 (40%)
Surgery followed by adjuvant RI	4/16 (25%)*
RI + rituximab	5/11 (45%)
RI + cytotoxic chemotherapy	3/24 (17%)
Any RI containing 1st-line Regimen	**32/101 (32%)**

* Out of patients who did not undergo surgical removal of the graft.

Table 4

Predictors of response to RI in patients treated with RI alone (n=67)

Response to RI		
Variable	**OR (95% CI)**	**P-value**
Patient characteristics		
Age at diagnosis	0.95 (0.92,0.99)	**0.006**
Transplanted organ (kidney vs. non-kidney)	1.615 (0.59,4.45)	0.354
Late (≥1 yr) vs. Early (<1yr)	0.889 (0.48,1.66)	0.711
>1 previous allograft	8.996 (1.01,79.92)	**0.049**
Pathologic characteristics		
Monomorphic vs. Polymorphic	0.433 (0.15,1.26)	0.124
EBV-positive vs. EBV-negative	0.762 (0.24,2.39)	0.641
Clinical Presentation		
B symptoms	0.478 (0.17,1.34)	0.161
Stage	0.609 (0.39,0.95)	**0.0306**
Single vs. Multiple Sites	0.31 (0.09, 1.05)	0.061
Bulky disease	0.103 (0.01,0.87)	**0.037**
Extranodal disease	0.65 (0.21,1.99)	0.451
Anorexia as initial symptom	0.27 (0.09,0.84)	**0.024**
Lab abnormalities		
Abnormal LDH	0.424 (0.14,1.27)	0.126
Anemia	0.635 (0.15,2.64)	0.531
Thrombocytopenia	0.951 (0.28,3.25)	0.935
Management		
Partial vs. Complete RI	0.921 (0.28, 3.03)	0.893
Multivariate Analysis		
Bulky disease	0.09 (0.008,0.97)	**0.048**
Stage	0.58 (0.33,1.003)	0.051
Age at diagnosis	0.94 (0.89,0.98)	**0.002**

Odds ratios (ORs) are presented with 95% confidence intervals (CI) for predictors of response. P-values<0.05 are in bold. Additional variables that were not found to be predictors of response include demographic parameters, presenting symptoms other than anorexia, specific organ involvement (including BM and CNS), hepatitis serostatus and additional lab abnormalities (data not shown).

Table 5

Predictors of mortality in patients treated with RI alone (n=67)

Survival		
	RI alone (n=67)	
Variable	**HR (95% CI)**	**P-value**
Patient characteristics		
Age at diagnosis	1.059 (1.03,1.09)	**<0.0001**
Year of diagnosis (<2000 vs. ≥2000)	0.961 (0.49, 1.88)	0.907
Transplanted organ (kidney vs. non-kidney)	0.635 (0.32,1.26)	0.191
Hep. B	1.033 (0.35, 3.02)	0.952
Hep. C	3.75 (1, 14.06)	**0.05**
Hep. B or Hep. C	1.281 (0.42, 3.92)	0.665
Late (≥1 yr) vs. Early (<1yr)	1.137 (0.77,1.68)	0.519
Pathologic characteristics		
Monomorphic vs. Polymorphic	1.159 (0.60,2.25)	0.662
EBV-positive vs. EBV-negative	0.781 (0.38,1.61)	0.502
Clinical presentation		
B symptoms	2.04 (1.01,4.10)	**0.046**
Weight loss	2.03 (1.08,3.82)	**0.028**
Dyspnea	2.68 (1.17,6.13)	**0.02**
Stage	1.269 (0.96,1.67)	0.09
Single vs. Multiple sites	1.815 (0.83, 3.97)	0.136
Bulky disease	1.06 (0.44,2.56)	0.9
Extranodal disease	1.675 (0.77,3.65)	0.194
CNS involvement	1.378 (0.18, 10.2)	0.75
BM involvement	3.404 (1.05, 11)	**0.041**
Liver involvement	2.79 (1.26,6.20)	**0.012**
Management		
Partial vs. Complete RI	0.981 (0.45,2.15)	0.96
Lab abnormalities		
Renal failure	2.05 (0.99,4.23)	0.052
LDH > ULN	1.821 (0.88,3.78)	0.108
LDH > 2.5 × ULN	5.97 (2.51,14.23)	**<0.0001**
Anemia	2.227 (0.78,6.33)	0.133
Thrombocytopenia	0.676 (0.33,1.40)	0.29

Hazard ratios (HRs) are presented with 95% confidence intervals (CI) for predictors of survival. P-values<0.05 are in bold. Additional variables that were not found to predict survival include other demographic parameters, presenting symptoms, lab abnormalities and organ involvement other than listed in the table (data not shown).