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Original Article

Ultra-Early Onset Post-Transplantation Lymphoproliferative Disease

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ABSTRACT. Post-transplant lymphoproliferative disease **(**PTLD) can present as early as days to as late as several decades after transplantation. This study, however, tries to research PTLD characteristics including histopathological and clinical features, predictors and prognosis of the disease when occurring within the first month post-transplantation. We conducted a comprehensive search for the available data using the Pubmed and Google scholar search engines for reports indicating presentation time in PTLD patients. Data from 25 previously published studies were included in the analysis. Finally, we found 355 recipients of organs presenting with "ultra-early onset PTLD." Transplant recipients with ultra-early onset PTLD were significantly more likely to have kidney allografts (P = 0.032). Transplant recipients with ultra-early onset PTLD were comparable to their counterparts in the control group in their demographics, histopathological findings and survival. Patients with ultra-early onset PTLD were significantly more likely to receive induction therapy (100% vs. 49%, respectively; P = 0.013). Pancreas transplant recipients were at a significantly higher risk for development of ultra-early onset PTLD (20% vs. 1%, respectively; P <0.001). Our findings emphasize the importance of immunosuppression potency as well as the type of allograft transplanted on the incidence of PTLD in the early stages after transplantation. However, we found no histopathological or outcome disparities for patients with ultra-early PTLD compared with controls. Further prospective studies with more comparable approaches to the patients are needed to confirm our findings.

Introduction

Post-transplantation lymphoproliferative disorders (PTLDs) represent a potentially fatal heterogeneous group of pathologic proliferation of B- or T-cells in the lymphoid tissue and neoplasia that commonly occur in organ transplant recipients in the poor cytotoxic T-cell function setting as a result of pharmacological immunosuppression as well as Epstein Barr virus infection.[1-4] It is speculated that organ recipients are at a substantial increased risk for developing PTLD, especially during the very early periods post-transplantation; the estimated ratio for this increased risk for PTLD development is about 25- to 500-fold higher

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than that in the normal population just within the first year after transplant.[5] The incidence of PTLD ranges from 1 to 20%,[6-9] depending on the type of allograft transplanted, the immunosuppression type and intensity, viral infections [particularly Epstein-Barr virus (EBV)], underlying disease and age.[10,11]

The time interval between transplantation and onset of PTLD is reported as one of the most relevant characteristics of the disease playing a major role in predicting the behavior of PTLD as well as the survival of patients.[12-16]

Based on their research findings, some investigators speculated that EBV-positive transplant recipients presented with PTLD earlier post-transplantation than those with EBV-negative serology.[17,18]

PTLD generally manifests during the first post-transplant year.[17-19] PTLD can present as early as less than 1 month to as late as several years after transplantation. Although early-onset PTLDs frequently have a favorable outcome, late-onset PTLDs are thought to behave more like aggressive lymphoma.

The small number of cases encountered at the different medical centers and the lack of a reliable, unequivocal classification together with the absence of multi-institutional prospective studies renders it hard to have a clear view on the different characteristics of the disease to develop treatment or preventive protocols. In our three previous reports, we studied early- and late-onset PTLD in renal and liver transplant recipients.[14-16]

The aim of this study is to determine the PTLD characteristics including histopathological and clinical features, predictors and prognosis of the disease when occurring within the first month post-transplantation.

Materials and Methods

We conducted a comprehensive search for the available data using the Pubmed and Google scholar search engines for reports of lymphoproliferative disorders occurring in transplant patients with regard to the disease presentation time. Keywords used for this purpose included "lymphoproliferative disorders + transplantation + early onset," "lymphoproliferative disorders + transplantation late onset," "lymphoproliferative disorders + transplantation + presentation time," "lymphoproliferative disorder + transplantation + time to PTLD," "PTLD + early onset," and "PTLD + late onset." In cases for which we were not able to achieve the full text of the articles, e-mails were sent to the correspondent authors requesting for the articles. Then, we only included studies in which data of each patient was presented separately. To minimize selection bias, we only included studies reporting their series of patients from single or multicenter populations, and studies with any specific selection criterion were excluded from the analysis. Moreover, only studies that had patients in both the two groups of ultra-early and control PTLD patients were included in this analysis. A standard questionnaire was developed to collect data from the different published studies. Finally, data from 25 previously published studies from various countries[12,20-43] were included into the study. The time between transplantation and PTLD onset was defined as the period between the graft and the first signs of PTLD or diagnosis, based on the methodology of the studies. Patients who presented with PTLD within the first 1 month after transplantation were considered as "ultra-early onset PTLD" and patients with PTLD that developed after this time were included in the study as controls.

Overall, 355 recipients of organ transplant who developed PTLD through their treatment course were included in this analysis. Patients' status regarding EBV infection was documented in 204 (57.5%) patients, of whom 179 (87.7%) were reported positive.

Because data used for this study were from studies of different methodology, we could not get all data we needed for the included patients. Disseminated lymphoma was diagnosed in 19 (12.8%; 206 missing data) patients when it was declared by the authors or at least three different organs were involved by PTLD (different lymph node areas were excluded from analysis due to lack of knowledge on how to categorize). Multi-organ involvement, defined

as involvement of more than one unique organ as well as more than one lymphatic region, was available in 64 (31.5%; 152 missing data) patients.

At lymphoma diagnosis, all patients had been receiving immunosuppressive regimens consisting of varying combinations of azathioprine, prednisone, cyclosporine, mycophenolate mofetil and antithymocyte/lymphocyte globulin (ATG/ALG) and OKT3. More and less, a rather uniform approach was used to manage all PTLD patients in the included reports. On diagnosis of PTLDs, the first step in almost all reports was to decrease or discontinue immunosuppressive therapy; different regimens of chemotherapy with or without surgical interventions were also used for some of patients.

Response to treatment was defined as any favorable change in the cancer measures as well as patients' clinical condition. Data of PTLD response to treatment were reported by the authors for 122 (34.4%) patients, of whom 86 (24.3%) responded to anti-malignancy treatment. However, we developed new criteria for defining the remission rates for the study population - while a remission episode was defined when patients were alive after their 24^{th} month of PTLD diagnosis (because all reported cases having this criterion had at least one confirmed remission episode), a no remission episode was defined when a patient died within the first month post-PTLD diagnosis (because among the reported cases there were no patients dying at the first post-transplant month and reported to have any remission episodes). According to these criteria, 185 (52.1%) patients had data on remission, of whom 119 (64.3%) had at least one response to treatment, irrespective of their future disease manner. The overall mortality was 165 patients (46.5% of the study population and 57.1% of the reported cases; 66 patients had missing data). Death due to PTLD was defined (1) when the authors stated it, (2) when the patient died within 6 months post-diagnosis or (3) when patients died due to PTLD treatment complications. Overall, 106 patients (48% of the reported data; 64.2% of the whole mortality rate) died due to the disease based on the above-mentioned criteria.

Statistical Analysis

We used SPSS v.13.0 for the statistical analyses. Statistical differences between patients' subgroups were performed using the χ^2 and Fishers' exact tests for proportions and the Student's t-test for continuous data. Survival analysis was performed with life tables and Kaplan - Meier methods and log - rank test. The statistical significance level was set at $P < 0.05$.

Results

Overall, 355 patients with PTLD were entered in the analysis (51 missing data). There were 196 (64.5%) male and 108 (35.5%) female patients. The mean age at diagnosis of PTLD was 38.6 ± 19.1 years. The mean interval between transplantation and the diagnosis of PTLD was 26.9 ± 39.3 months, whereas the follow-up time after diagnosis of PTLD was 20.4 ± 30.5 months.

Characteristics of the patients regarding their malignancy onset time are summarized in Table 1. Organ transplant recipients with ultra-early onset PTLD were significantly kidney-transplant patients ($P = 0.032$), and they were comparable to their counterparts in the control group in their gender make up ($P = 0.553$), lymphoma cell types ($P = 0.596$), remission episodes ($P = 0.823$), EBV-positive test results ($P = 0.728$), total mortality rate ($P = 0.684$), death due to the PTLD (according to the defined criteria described in the methods section; $P = 1.0$), multiorgan involvement (according to the defined criteria; $P = 1.0$) and disseminated PTLD (according to the defined criteria; $P = 0.633$). Table 2 summarizes the different organ involvements by PTLD occurring in the transplant patients regarding the time of PTLD onset.

Transplant recipients with ultra-early and control PTLD patients were comparable in their age at the time of transplantation (median age 32.0 vs. 41.0 years; $P = 0.323$). Histopathological evaluations of specimen achieved

Table 1. Comparison of the characteristics of transplant recipients with ultra-early and control post-transplant lymphoproliferative disease (PTLD) groups.

Variables	Ultra-early onset	Controls	Significance	Available data
Age (years)	35.4 ± 16.9	38.9 ± 19.3	0.323	326
Pediatric; <18 years old (%)	4 (12.9)	55 (18.6)	0.624	326
Gender male (%)	21 (70.0)	175 (63.9)	0.553	304
Time to PTLD development (months)	0.9 ± 0.24	29.7 ± 40.4		355
Multiorgan involvement (%)*	5 (29.4)	59 (31.7)	1.0	203
Disseminated PTLD (%)*	2 (18.2)	17 (12.3)	0.633	149
Hodgkin disease (%)	1 (7.1)	6 (4.1)	0.860	159
EBV status (%)	18 (90)	149 (87.1)	1.0	191
Remission episode (%)	15 (62.5)	104 (64.6)	0.823	185
Use of induction therapy	7 (100)	46 (48.9)	0.013	101
Monoclonal lesions vs. polyclonal (%)	4 (57.1)	51 (69.9)	0.671	80
Monomorphic lesions (%)	3 (16.7)	44 (31.0)	0.277	160
Lymphoma cell type B-cell (%)	12 (100)	103 (91.2)	0.596	125
Mortality rate	14 (51.9)	151 (57.6)	0.684	289

*According to the criteria defined in the methods section, **IS: Immunosuppression

Table 2. Frequency of the involved organs in 224 transplant recipients with ultra-early and control PTLD patients.

Involved organs	Ultra-early onset	Controls	Significance
Skin	0	5 (2.5)	1.0
Stomach	0	2 (1.0)	1.0
Genitalia	0	2 (1.0)	1.0
CNS	2 (8.7)	13 (6.5)	0.657
Spleen	1 (4.3)	2 (1.0)	0.279
Colon	1 (4.3)	10 (5.0)	1.0
Small intestine	3 (13.0)	17 (8.5)	0.441
Renal involvement	5 (21.7)	14 (7.0)	0.032
Liver involvement	2 (8.7)	19 (9.5)	1.0
Respiratory system	2 (8.7)	26 (12.9)	0.747
Bone marrow	0	11 (5.5)	0.609

from the PTLD lesions showed comparable results for ultra-early and control PTLD patients with regard to their clonality (P = 0.671), morphology (P = 0.277) and ratio of Hodgkin and Hodgkin-like disease (P = 0.860). In addition, patients with ultra-early onset PTLD significantly received induction therapy (100% vs. 49%, respectively; P = 0.013). Table 3 shows the associations between type of allograft and time of PTLD onset. Pancreas transplant recipients were at a significantly higher risk for the development of ultra-early onset PTLD (20% vs. 1%, respectively; P <0.001).

At the last follow-up, 165 (57%) patients were

Table 3. Allograft types in 322 PTLD with ultra-early and control patients whose data were included in the analysis.

Allograft type	Ultra-early onset	Controls	Significance
Renal allograft	13 (43.3)	103 (35.3)	0.426
Liver allograft	4 (13.3)	85 (28.8)	0.085
Heart allograft	1 (3.3)	37 (12.7)	0.229
Lung	3 (10.0)	25 (8.6)	0.735
Pancreas	6 (20.0)	4 (1.4)	0.0001
Bone marrow	3 (10.0)	38 (13.0)	0.780

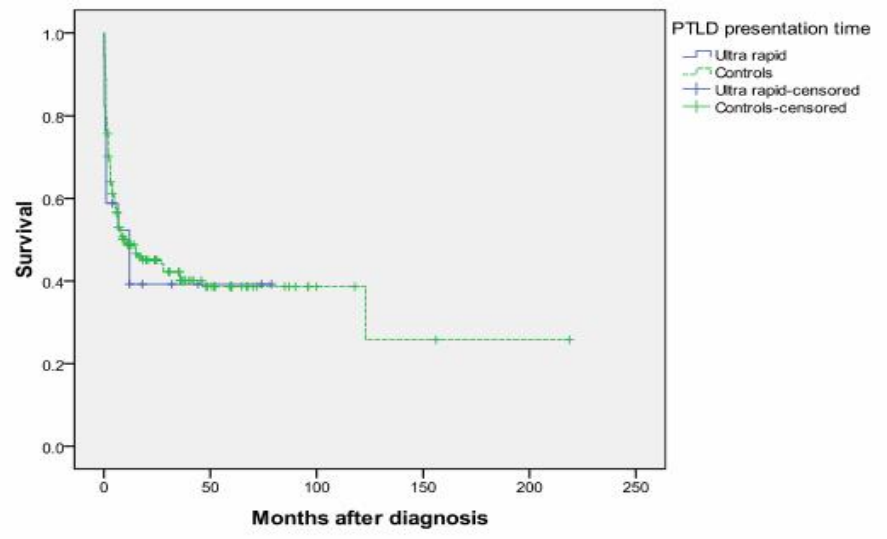

Figure 1. Survival curves of PTLD patients regarding presentation time, when death irrespective of the reason is defined as the outcome.

dead (66 missing data). When death irrespective of the reason was used as the final outcome, the log - rank test did not show any difference between the two groups in their survival (P = 0.582; Figure 1). Moreover, no statistically significant difference was observed between the two groups when death only due to PTLD was used as the final outcome (based on the defined criteria in the methods section; P = 0.236; Figure 2). The 1- and 5-year survival rates for the ultra-early onset PTLD patients were 52% and 37%, respectively, compared with 48% and 38% for the control group.

Discussion

PTLD is an ominous complication in organ

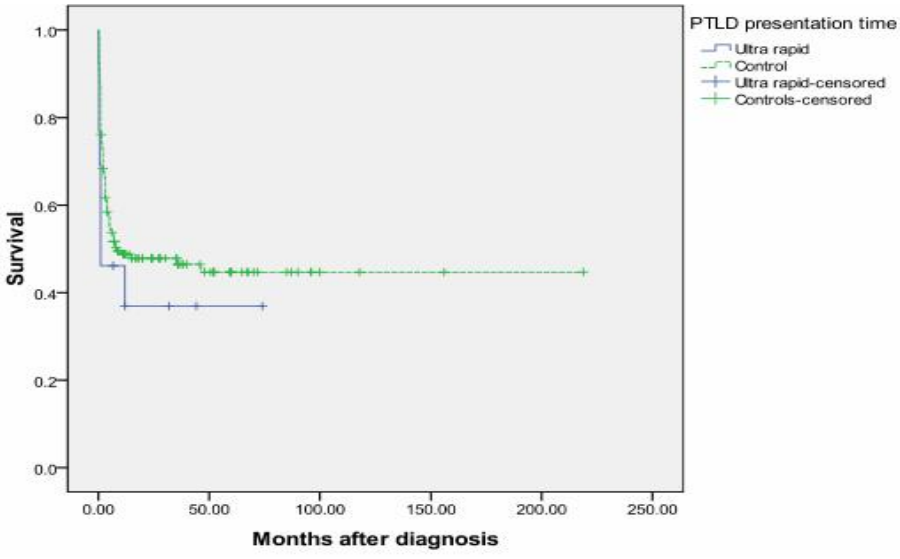

Figure 2. Survival curves of post-transplant lymphoproliferative disease (PTLD) patients regarding their presentation time, when death due to PLTD is considered as the outcome.

transplant recipients, and it seriously threatens their health and life.[44] PTLD usually presents with uncontrolled B-cell proliferation, with histopathological features that range from polymorphic cellular expansion of lymphocytes of any size to monomorphic large cell non-Hodgkin lymphomas. The incidence and natural pathways have a very wide range depending on the immunosuppression used, viral infections and the organ transplanted,[4,45-50] with the highest incidence in recipients of small bowel, heart–lung, lung and T-cell-depleted bone marrow transplants (with an up to 30% incidence rate to 1 - 5% in kidney and liver allograft recipients).[47,49,51,52] With the newly introduced highly potent immunosuppressants aiming at prevention of graft rejection, the frequency of PTLD has dramatically increased.[47] Furthermore, the interval between transplantation and the onset of PTLD has also decreased.[47]

PTLD may occur at any time after transplantation and present as early as days and as late as decades post-transplantation.[3,14,15,53] However, the general belief is that the highest risk of PTLD development is within the early post-transplant period, conceptually due to the higher doses of immunosuppression.[11] There is a general consensus on categorizing PTLD based on the time interval between transplantation and PTLD to early- and late-onset PTLD, with early-onset PTLD emerging within the first year post-transplantation and late-onset PTLD presenting beyond that time.

In our study, PTLD that occurred within the first month post-transplantation had comparable histopathological features and survival in comparison with other PTLD patients. However, we found that use of induction therapy was significantly associated with ultra-early development of PTLD. This finding is consistent with our previous knowledge on the impact of highly potent immunosuppression on the incidence of PTLD at the early period post-transplantation. Using the Collaborative Transplant Study database, Opelz et al. found that treatment with ATG/ALG or OKT3 increases the risk of lymphoma only during the first year after transplantation, whereas the risk was similar to that in non-antibody-treated patients in the subsequent years.[12] Our study impressively confirms this concept, while all PTLD patients who presented with the disease before the end of the second month post-transplantation had a history of induction therapy (P = 0.009).

Evidence suggests that the type of organ transplanted has a substantial impact on the incidence and behavior of PTLD; the incidence of PTLD is reported to be high in small bowel, heart–lung, lung and T-cell-depleted bone marrow transplants but low in renal and liver transplant recipients.[11,47,51-53] In this study, we found that recipients of pancreas and pancreas - kidney transplants are at a significantly higher risk for developing PTLD within the first month post-transplantation.

However, our study has some limitations. First, it is data collection from different institutions of a retrospective nature. Because of the different approaches employed by the 25 included series, we could not gather all data for any individual variable for having a perfect view on the whole population; e.g., categorization of the histological features of the PTLD were not based on the same method therefore we invented some new methods to maximize inclusion of patients from various studies. On the other hand, data presentation was not perfect in all the articles; e.g., while some series reported very distinct data on their treatment methods or PTLD involvement sites, others presented very limited and ambiguous data or even nothing. Methods of data ascertainment were also different between the different reports. For example, for evaluation of EBV infection status, some of the studies used simple serological evaluations while others used polymerase chain reaction methods.

In conclusion, in this study, we found that transplant recipients are at a greater risk of developing ultra-early PTLD within the first month post-transplantation, especially in pancreas and kidney allograft recipients. Ultra-early PTLD is usually of a polyclonal and polymorphological nature, and more of a B-cell type. No outcome differences were found between early and late PTLD.

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