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# Early and Late Posttransplant Lymphoproliferative Disorder After Lung Transplantation—34 Cases From the European PTLD Network

Jaksch et al. (*1*) have recently reported a low incidence of posttransplant lymphoproliferative disorder (PTLD) of B-cell origin after lung transplantation (18 in a series of 1157 [1.6%] consecutive patients) in Vienna. Their findings show that posttransplantation management is crucial to PTLD prevention and document the effectiveness of the program in Vienna. The authors hypothesize that their use of anti-cytomegalovirus (CMV) immunoglobulin prophylaxis (Cytotect, 1 mL/kg intravenously on days 1, 7, 14, and 21 postoperatively) protects patients from Epstein-Barr virus (EBV)–associated PTLD. This hypothesis is based on the findings by Opelz et al. (*2*) who had observed no cases of PTLD within the first year after transplantation in 2103 kidney transplant recipients who had received anti-CMV immunoglobulin prophylaxis for 4 months after transplantation—significantly less than in an untreated control group. However, in the subsequent 5 years, new cases of PTLD developed at similar rates in the examined groups with and without CMV prophylaxis.

We were intrigued by the low proportion of late PTLD reported (only 3 of 18 cases occurred >1 year after transplantation) and analyzed time-to-PTLD in lung transplant recipients in the PTLD-1 (*3*) and PTLD 1–3 (*4*) trials as well as those treated at Hopital Pitie-Salpêtriere, Paris, or reported to the German PTLD registry. Overall, 34 patients with PTLD after lung transplantation were included from centers in Australia, Austria, Belgium, France, and Germany. Twenty-two of 34 had received lung transplants and 12 of 34 had received combined heart/lung transplants between 1988 and 2011. Strikingly, in both groups, less than 40% of cases occurred in the first year after transplantation (early PTLD) (Table 1). We observed cases later than 2 years (16 of 34 [47%]), 5 years (10 of 34 [29%]), and 10 years (6 of 34 [18%]). Furthermore, 6 of 31 patients with PTLD after lung or heart/lung transplantation evaluated for EBV association had EBV-negative disease by EBV-encoded RNA in situ hybridization. These included two cases of diffuse large B-cell lymphoma (DLBCL)-PTLD

**TABLE 1.** Time to PTLD in lung transplant recipients reported to the European PTLD network

| Transplanted organ | n | Male, n (%) | Transplant year: Median (range) | Time to PTLD: Median (years) | Time to PTLD: Range (years) | Time to PTLD: Early | Histology (PTLD subtype) | EBV association[a] |
|---|---|---|---|---|---|---|---|---|
| Lung and heart/lung | 34 | 16 (47%) | 2001 (1988–2011) | 1.83 | 0.14–23.43 | 12/34 (35%) | 22 DLBCL PTLD<br>1 PBL PTLD<br>2 MZL PTLD<br>2 Plasmacytoma-like PTLD<br>2 Polymorphic PTLD<br>2 Lymphoplasmocytic PTLD<br>1 Hodgkin PTLD<br>2 unknown | 25/31 |
| Lung | 22 | 11 (50%) | 2001 (1989–2011) | 3.98 | 0.14–13.76 | 8/22 (36%) | 13 DLBCL PTLD<br>2 MZL PTLD<br>2 Plasmacytoma-like PTLD<br>2 Polymorphic PTLD<br>2 Lymphoplasmocytic PTLD<br>1 Hodgkin PTLD | 17/21 |
| Heart/lung | 12 | 5 (42%) | 2001 (1988–2010) | 1.30 | 0.28–23.43 | 4/12 (33%) | 9 DLBCL PTLD<br>1 PBL PTLD<br>2 unknown | 8/10 |

[a] EBV data missing in three cases.
MZL, marginal zone lymphoma; PBL, plasmablastic lymphoma.

and one case each of marginal-zone PTLD, plasmacytoma-like PTLD, plasmablastic PTLD, and lymphoplasmocytic PTLD (median time-to-PTLD, 7.6 years; range, 3.8–12.0 years).

In comparison with our cases and the data of Opelz et al. (*2*), the key observation of Jaksch et al. (*1*) is the low proportion of late (and EBV-negative) PTLD in their transplant cohort. It is therefore possible to speculate that this effect was achieved not only through early administration of CMV immunoglobulin but by optimized immunosuppression throughout follow-up, potentially aided by monitoring of CMV polymerase chain reaction. A reduction of PTLD incidence through viral load monitoring (of EBV viral load) and immunosuppression alteration has previously been demonstrated after heart (*5*) and pediatric liver (*6*) transplantation. The test of this hypothesis will be the future incidence of late PTLD in the Vienna cohort.

We would like to note that the differences between our cases and the cohort presented by Jaksch et al. might to some extent reflect selection bias (patients referred to a hematologist for treatment). Furthermore, we did not control for PTLD risk factors such as EBV serostatus at transplantation.

Median overall survival of PTLD after lung transplantation was 1.1 years in the 18 patients reported by Jaksch et al. (*1*). We observed a median survival of 1.2 years for both our entire cohort of 34 patients and the subgroup of 22 lung transplant recipients. In addition, the four lung transplant recipients treated with sequential therapy (rituximab and CHOP chemotherapy) in the PTLD-1 trial (*3*) achieved a similarly poor median overall survival of only 1.0 years compared with a median overall survival of 6.6 years for the entire trial cohort of 70 patients with PTLD. This reinforces the need for both effective prophylaxis of and improved treatment strategies for PTLD after lung transplantation.

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