ELSEVIER

The Journal of Heart and Lung Transplantation
http://www.jhltonline.org

Post-transplant lymphoproliferative disease in heart and lung transplantation: Defining risk and prognostic factors

Gayathri Kumarasinghe, MBBS, FRACP,[a] Orly Lavee, MBBS, FRACP,[b] Andrew Parker, MBBS, FRCPA,[c] Ian Nivison-Smith, MAppStat, PhD,[b] Samuel Milliken, MBBS, FRACP,[b] Anthony Dodds, MBBS, FRACP,[b] Joanne Joseph, MBBS, FRACP,[b] Keith Fay, MBBS, FRACP,[b] David D. Ma, MBBS, FRACP,[b] Monique Malouf, MBBS, FRACP,[a] Marshall Plit, MBBS, FRACP,[a] Adrian Havryk, FRACP, PhD,[a] Ann M. Keogh, MBBS, FRACP,[a] Christopher S. Hayward, MBBS, FRACP,[a] Eugene Kotlyar, MBBS, FRACP,[a] Andrew Jabbour, FRACP, PhD,[a] Allan R. Glanville, MBBS, FRACP,[a] Peter S. Macdonald, FRACP, PhD,[a] and John J. Moore, MBBS, FRACP, FRCPA[b]

From the [a]Heart Lung Transplant Unit, St Vincent's Hospital, Sydney, New South Wales, Australia; Departments of [b]Haematology; and [c]Anatomical Pathology, St Vincent's Hospital, Sydney, New South Wales, Australia.

KEYWORDS:
PTLD;
heart transplant;
lung transplant;
post-transplant malignancies

BACKGROUND: Heart and lung transplant recipients have among of the highest incidence rates of post-transplant lymphoproliferative disease (PTLD). Despite this, there is a paucity of data specific to this group. We collated data on heart, lung and heart–lung transplant recipients with PTLD to identify disease features and prognostic factors unique to this group of patients.

METHODS: Seventy cases of PTLD were identified from a single institution (41 heart, 22 lung, 6 heart–lung and 1 heart–kidney transplant) from 1984 to 2013. Demographics, immunosuppression, treatment, response, complications and survival data were analyzed. Uni- and multivariate Cox regression analyses were performed to identify prognostic factors.

RESULTS: The incidence of PTLD was 7.59% in heart–lung, 5.37% in heart and 3.1% in lung transplant recipients. Extranodal disease (82%) with diffuse large B-cell lymphoma (72%) was the most common presentation. Bone marrow involvement (13%) and central nervous system disease (3%) were uncommon. Heart transplant recipients had later onset of PTLD (>1 year post-transplant), with less allograft involvement, compared with lung and heart–lung recipients. Poor prognostic markers were bone marrow involvement (HR 6.75, $p < 0.001$) and serum albumin <30 g/liter (HR 3.18, $p = 0.006$). Improved survival was seen with a complete response within 3 months of treatment (HR 0.08, $p < 0.001$). Five-year overall survival was 29%.

The first 2 authors (G.K. and O.L.) share first authorship.

Reprint requests: John J. Moore, MBBS, FRACP, FRCPA, Department of Haematology, St Vincent's Hospital, Victoria Street, Darlinghurst, NSW 2010, Australia. Telephone: +61-2-8382-1111. Fax: +61-2-9355-5602.
E-mail address: john.moore@svha.org.au

1053-2498/$ - see front matter
http://dx.doi.org/10.1016/j.healun.2015.05.021

CONCLUSION: This analysis is the largest to date on PTLD in heart and lung transplant recipients. It provides a detailed analysis of the disease in this group of patients and identifies unique prognostic features to aid risk stratification and guide treatment allocation.

J Heart Lung Transplant 2015;34:1406–1414

Post-transplant lymphoproliferative disease (PTLD) is comprised of a group of pathologically and clinically heterogeneous disorders occurring in immunosuppressed patients who have undergone organ transplantation.[1] As a group, the diseases represent one of the most serious complications of solid-organ transplantation, with mortality ranging between 50% and 70% in most studies.[2–7] Immunosuppressive therapy required to prevent allograft rejection compromises anti-tumor and anti-viral immunosurveillance in patients who develop PTLD.[8–10] Many cases are directly attributable to infection or reactivation of Epstein–Barr virus (EBV) and subsequent impaired cytotoxic T-cell immunity.[11–16]

Patients who receive heart and lung transplants have a higher overall incidence of PTLD between 3% and 9%, compared with 1.4% to 2.9% in renal and 0.9% to 2.6% in liver transplantation.[1–3,17–20] Thoracic organ transplant recipients are also heavily immunosuppressed, commonly have a complicated post-transplant course, and often present with extensive lymphoproliferative disease. Despite this, there is a relative paucity of data pertaining specifically to outcomes and prognostic factors for heart and lung transplant patients within the PTLD literature.[21–24]

Since the first description of PTLD around 40 years ago, there have been significant paradigm shifts in understanding the pathogenesis underpinning PTLD, diagnostic processes and the management of this complex set of diseases.[25] Reduction of immunosuppression in the first instance remains a mainstay of management in patients diagnosed with PTLD, although enduring remissions are uncommon.[26,27] The role of rituximab-based regimens is starting to become more defined in B-cell lymphoproliferative disorders because these lymphomas express CD20 and treatment with rituximab is considered relatively non-toxic compared with traditional chemotherapeutic agents. The PTLD-1 trial, a prospective Phase II trial using rituximab in sequential immunochemotherapy, also strongly supports its use in treating B-cell PTLD.[26] These new advances are driving an interest in identifying risk and prognostic factors for specific susceptible patient groups.[26–29]

In recent publications focusing on these areas, heart and lung transplant patients constituted a minority of the patient sample, and hence the unique characteristics of this patient group have not been described in detail. A landmark study analyzing prognostic factors in PTLD included 8 (10%) heart and 5 (6%) lung transplant recipients in the cohort.[5] Recently, there have been more studies focusing on thoracic organ transplantation with sample sizes ranging from 2 to 65 patients, mainly focusing on disease description and risk factors, with less emphasis on identifying treatment and prognostic factors.[30–34]

To provide a better description of this group we present a detailed retrospective analysis of 70 cases of PTLD in thoracic organ transplantation from a cohort of 1,490 transplants at a single center. We describe patient demographics, risk factors, management and outcomes to understand the unique clinical features of this disease and to further develop tailored treatment strategies and prophylaxis.

Methods

This was a retrospective study using data from a single heart and lung transplant institution. Patients were identified by entries of PTLD in the institution's transplant database. Patients transplanted between January 1984 and December 2010, and diagnosed with PTLD between January 1984 and December 2013, were included in the study. The diagnosis of PTLD was verified through assessment of tissue biopsies as reported by experienced hematopathologists.

We collected detailed data on patient demographics, disease characteristics, treatment regimens and response to therapy by review of patient medical records, laboratory results, chemotherapy records and data from the institution's transplant database. Histopathology samples were re-analyzed for consistency of reporting. The outline of the study is detailed in Figure 1. Of the 70 PTLD cases identified, 10 patients had incomplete data for PTLD disease characteristics and treatment, and hence were only included in baseline demographics analyses and survival calculations. This study was approved by our institution's human research ethics committee (SVH HREC 11/202).

Definitions and classification

PTLD was classified on histopathology according to the 2008 World health Organization's Classification of Tumours of Haematopoietic

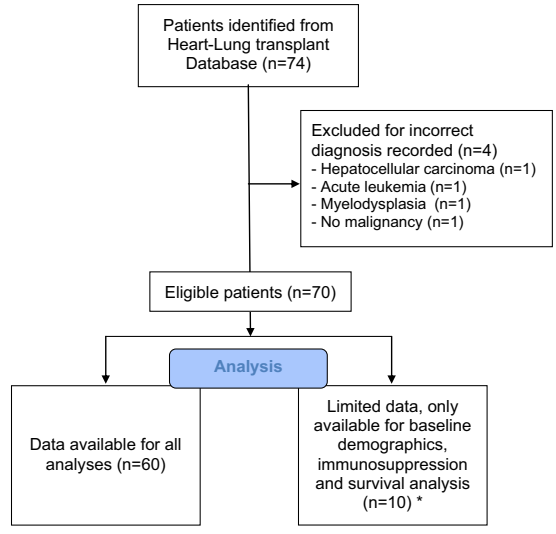

Figure 1 Study outline.