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Clinical trial paper

Observational study of lung transplant recipients surviving 20 years

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ABSTRACT

Background: Lung transplant recipients have reduced long-term survival compared with other solid organ recipients. There is a lack of published data on the characteristics of very long term survivors.
Methods: We describe the demographics, clinical history and post-procedure function of all lung transplant recipients who have survived greater than 20 years at our centre.
Results: At the time of analysis there were 21 (16.4%) of 128 patients who survived over 20 years. The mean age at transplantation was 31.8 ± 9.9 years. Five of 21 had undergone single-lung, eight double-lung and eight heart-lung transplant procedures. At the last evaluation, mean percentage predicted FEV1 in recipients of single and double lung were 51.3% and 57.9% respectively. By 20 years, 19 (90.5%) patients had developed bronchiolitis obliterans syndrome (BOS) with three (14%) BOS 1, six (29%) BOS 2 and 10 (48%) BOS 3 and two (9.5%) free from BOS. The median time to onset of BOS was 9.7 years (range 1.6–17.9). Of eight patients (38%) who required renal replacement, four (19%) had successfully undergone renal transplantation and four (19%) were on haemodialysis. Only one patient (5%) had symptomatic osteoporosis. Nineteen patients (90%) were treated for hypertension. Five patients (24%) had diabetes, all with an underlying diagnosis of cystic fibrosis and four of them developing diabetes post operatively.
Conclusions: In our experience, 20-year survivors of lung transplantation had a delayed onset of BOS and morbidities due to immunosuppression that can be appropriately managed leading to long-term survival.

1. Introduction

Lung transplantation has become the standard of care in the management of end-stage lung disease in carefully selected patients, who otherwise have poor short-term survival [1]. The current median survival is 5.7years with 32% of lung transplant recipients alive at ten years [2]. There remains a paucity of published data and reported experiences from centres on the natural history of lung transplant patients surviving longer than 10 years. Rutherford et al. in 2005 evaluated all 10 year lung transplant survivors at our centre in terms post-transplant complications, functional status and quality of life (QoL) utilising SF-36 questionnaire. A late onset or an absence of bronchiolitis obliterans syndrome (BOS) with preserved mental but diminished physical health in QoL was seen in these select patients [3].

Compared to other solid organ transplantations, prolonged survival following lung transplantation is reduced [4]. As our understanding of immunosuppression and overall management of post-transplant complications improves, we are seeing more lung transplant recipients living longer [5].

The development of BOS remains a significant factor in limiting long-term survival in lung transplant patients, with 50% of recipients having developed BOS by five years [2]. BOS is

Abbreviations: BOS, bronchiolitis obliterans syndrome; FEV1, forced expiratory volume in 1 s; TLI, total lymphoid irradiation; RRT, renal replacement therapy; SL, single lung; DL, double lung; HL, heart-lung; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease.

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characterised by irreversible airflow obstruction, with insidious onset of symptoms and progressive reduction in forced expiratory volume in 1 s (FEV_1) and mid-expiratory flow ($FEF_{25-75\%}$). BOS not only affects both the long-term survival of lung transplant patients but also causes loss of health-related quality of life [6]. The International Society for Heart and Lung Transplantation (ISHLT) registry reported BOS as a leading cause of mortality in survivors beyond five years [2].

Immunosuppression, whilst remaining fundamental to graft survival, causes a number of complications including infective, metabolic, endocrine, vascular and malignant diseases. The development of these complications adds to a recipient's morbidity, decreasing health-related quality of life.

Since the inception of the lung transplantation program in 1987, we now have a cohort of 21 patients who have survived 20 years or more. We describe the clinical status of all patients who have survived at least 20 years post lung transplantation at our institution.

2. Methods

The clinical records of all lung transplant patients who were transplanted and followed up at the Freeman Hospital, up to December 2013, who had survived greater than 20 years were analysed. We collected data as described previously and listed below [3]. At our centre, all double-lung and heart-lung transplantations were undertaken with the use of cardiopulmonary bypass (CPB). Single lung transplantations were undertaken with the aim of not using CPB, unless there was evidence of pulmonary hypertension, with right ventricular dysfunction with a drop in blood pressure when the pulmonary artery on one side was clamped or the development of hypercapnia leading to respiratory acidosis during transplantation making the use of CPB unavoidable.

The following were recorded for each individual patient:

1. Pre-transplant diagnosis and transplantation procedure performed.
2. Duration of survival (years) and cause of death.
3. All transbronchial biopsies performed as part of surveillance and as clinically indicated are described in terms of histology grades as per Lung Transplant Study Group.[1] Episodes of acute rejection was defined as acute clinical deterioration or histologically proven acute cellular rejection requiring augmentation with corticosteroids. Biopsy specimens not requiring augmentation with corticosteroids as deemed by the clinical team were not coded as acute rejection episodes.
4. Immunosuppression history
5. Presence and time to development of BOS and current BOS status at the most recent pulmonary function testing.[2] BOS management strategy included the use of immunosuppression, azithromycin and total lymphoid irradiation (TLI).
6. The 6-min walk distance (6MWD) performed in metres up to 11 years post-transplantation.
7. Serum creatinine (μmol/L) pre- and 1-, 5-, 10-, 15-, and 20 years post transplantation and at the most recent evaluation and requirement for renal replacement therapy (RRT).
8. Development of diabetes, osteoporosis associated with painful fractures,[3] hypertension, symptomatic ischaemic heart and cerebrovascular disease. Coronary angiogram results for heart-lung transplantation recipients for development of coronary artery vasculopathy.
9. Development of post-transplant lymphoproliferative disease and other malignancies.

3. Results

There were 128 patients who had undergone lung transplantation at Freeman hospital, prior to December 1993 and thus potential 20 year survivors in December 2013 when data collection first commenced. Of these, 21 (16.4%), eight females and 13 males, survived at least 20 years with an overall median survival of 21.3 (range 20.1–24.9) years. Eighteen (86%) patients were still alive at evaluation, with three (14%) deaths at 20.8, 21.5 and 24.5 years post transplantation. The cause of death was pneumonia in one patient and complications of BOS in the other two patients. Mean age of survivors at transplantation was 31.8 ± 9.9 years. The indications for transplantation and procedures performed are shown in Table 1. The mean age of donors was 29.0 ± 11.9 yrs, consisting of 12 females and 9 males. The mean difference in age between donor and recipient was 3 yrs (range 0–21yrs). There were no patients who had undergone retransplantation. Of all 128 patients from 1987 to December 1993, there were 8.1% (5/62) 20 year survivors following single lung transplantation, 25% (8/32) following double lung (DL) and 23.5% (8/34) following heart-lung (HL) transplantation, respectively. The mean duration of survival of all 128 patients was 7.0 yrs (range 0–24.9) (see Table 2).

3.1. Functional status

Mean percentage predicted FEV1 at latest evaluation in single lung recipients (n = 5) was 51.3% (range 46.1–64.7%) and in recipients of double lung or heart-lung blocks, n = 16 (DL plus HL) was 57.9% (range 28.5–92.1%) predicted. The mean percentage predicted FEV1 at ten and twenty years post lung transplantation in single lung recipients was 66.8% and 52.3% respectively and in recipients of two lungs was 78.9% and 58.6% respectively. Two (10%) patients had no evidence of BOS and three (14%) were BOS 1, six (29%) BOS 2 and 10 (48%) BOS 3. The median time to onset of BOS was 9.7 years (range 1.6–17.9) and patients had survived a median of 12.5 years since its onset. The effect of donor-recipient age mismatch was analysed by dichotomizing the cohort by mean age difference of three years and analysing the percentage predicted FEV1 at 20 years survival. Recipients within three years of their donors' age at transplantation had a mean percentage predicted FEV1 of 62.4 ± 16.8% whilst those with mismatch beyond three years had an FEV1% predicted of 51.1 ± 13.5%, which was not significant (p = 0.105). Fig. 1 shows the percentage of patients with freedom from BOS with years from transplantation, all lung transplants performed at Freeman until December 1993 and from the recent ISHLT registry. Fig. 2 shows the change in percentage predicted FEV1 over 20 years.

Treatments for BOS varied and comprised a switch from ciclosporin to tacrolimus at median time of 9.7years (range 4.6–15) in 12, azithromycin therapy commenced at a median time

[1] Patients underwent a scheduled surveillance bronchoscopy with transbronchial lung biopsy at 1 week and 1, 3, 6 and 12 months following lung transplantation and at times of clinical deterioration.

[2] The forced expiratory volume in 1 s (FEV1) was performed on SensorMedics Autobox 6200 SensorMedics Autobox 6200 (Sensor Medics Corp. California, U.S.A). BOS stage was determined according to International Society for Heart and Lung Transplantation (ISHLT) guidelines [7].

[3] Osteoporosis with fractures or T-score greater than two standard deviations below the predicted normal at bone densitometry was a contraindication for listing for lung transplantation. In this era, patients did not routinely have bone densitometry performed or receive osteoporosis prophylaxis post transplantation.