Supplementary File 1.

Immunosuppression

Our center's maintenance immunosuppression protocol includes cyclosporine with therapeutic drug monitoring and azathioprine 1.5-2 mg/kg/day. Maintenance corticosteroid dosing was administered as follows; methylprednisone 0.5mg/kg for 3 days followed by prednisolone 0.5mg/kg/day tapering to 0.25mg/kg/day at three months, 0.15mg/kg/day at six months and 0.075mg/kg/day at twelve months post-transplant. Basiliximab (20mg IV for 2 doses) was given to patients with early acute kidney impairment with temporary cessation of cyclosporine. Induction immunosuppression was not administered. Since 2008, patients with a positive virtual crossmatch, defined as a pre-transplant donor specific antibody, were treated with a post-operative desensitization protocol comprised of plasma exchange, intravenous immunoglobulin (IVIG: 1g/kg) and rabbit anti-thymocyte globulin (3-5mg/kg) (28). Patients with pre-transplant or de novo donor-specific HLA antibodies were treated with mycophenolate as a substitute for azathioprine. Symptomatic or spirometrically-significant A1, or any >= A2, acute cellular rejection was treated with augmented immunosuppression, most commonly with pulse corticosteroids.

Definition and Treatment for Chronic Lung Allograft Dysfunction (CLAD)

Baseline lung function was established as the average of the two best post-transplant FEV_1 measured at least 3 weeks apart. Low baseline FEV_1 was defined as failure to ever achieve >80%-predicted. CLAD was defined as a sustained (at least 2 FEV_1 values at least ≥ 3 weeks apart) and irreversible drop in FEV_1 to ≤ 80% of baseline. CLAD was calculated in an automated fashion and each case was subsequently confirmed by physician review. Patients were excluded from the CLAD analysis if they had <4 pulmonary function tests after

transplant. CLAD phenotyping with the 2019 consensus criteria was performed where longitudinal TLC and chest imaging data were available, as described previously. Cases of persistent lung allograft dysfunction without CLAD were determined by clinical review and infection was defined as positive bronchoalveolar lavage (BAL) culture.

At the onset of CLAD, patients were typically changed from cyclosporine to tacrolimus, initiated on a trial of azithromycin, and aggressively treated for gastroesophageal reflux. Re-transplantation was considered for appropriate candidates. No patients received Montelukast.

Statistical Analysis

Data were right censored at 23-Jun-2018 for survival analysis and the date of the last lung function test for CLAD analysis. Lung allograft dysfunction from causes other than CLAD were analyzed as censoring events. The normalized A cellular rejection score was calculated as the sum of each grade respectively divided by the total number of evaluable biopsies.