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Repeated human leukocyte antigen mismatches in lung re-transplantation

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ABSTRACT

Background: The role of HLA-sensitization in the absence of detectable DSA in lung re-transplantation is unclear. Antigens of the second donor matching the HLA typing of the first donor are considered 'unacceptable', by some tissue typing laboratories, especially in kidney re-transplantation.
Methods: Thus, we performed a retrospective analysis of all lung re-transplantations focussing on the impact of HLA-homologies between the first and the second donor ('unacceptable' antigens; repeated HLA mismatch) on patient and graft survival.
Results: A total of 132 lung re-transplantations were performed at our centre between 1985 and 2014, of which 120 with complete HLA data were analysed. 55.8% of the recipients received re-transplants with repeated HLA mismatched antigens whereas 43.2% of the re-transplants were transplanted without repeated HLA mismatched antigens.
Postoperative survival showed no difference between re-transplant procedures with or without repeated HLA mismatches ($p = 0.99$). While neither homologies on the HLA-A, -B, -C, or -DR locus, nor the addition of several locus homologies ($p = 0.72$) had an impact on survival, unexpectedly, repeated HLA mismatching on the HLA-DQ locus was correlated with better survival. Re-transplantations with repeated HLA mismatches did not result in more development of CLAD as compared to recipients without repeated HLA mismatches ($p = 0.99$). Neither the number of repeated HLA mismatched antigens ($p = 0.52$) nor the HLA locus (HLA-A($p = 0.34$), HLA-B($p = 0.97$), HLA-C ($p = 0.80$), HLA-DR($p = 0.49$) and HLA-DQ($p = 0.07$)) had an impact on the development of CLAD after re-transplantation.
Conclusion: Transplantation with repeated HLA mismatches due to sensitization by a previous transplantation in the absence of detectable HLA-antibodies does not have a negative impact on patient or graft survival.

1. Introduction

Lung transplantation remains the only effective therapy for various endstage lung diseases, however, chronic rejection, recently termed chronic lung allograft dysfunction (CLAD), continues to hamper long-term survival of patients after lung transplantation [1]. Remedies for CLAD are scarce, with azithromycin [2] or photopheresis merely stabilizing lung function [3,4], while lung re-transplantation constitutes the only definitive treatment [5].

In the early days of lung re-transplantation it was suspected that re-transplants are more susceptible to early development of chronic rejection than primary transplants [6] Evidence gathered since, however, indicates that the recurrence of CLAD after re-transplantation for chronic rejection is, at best, slightly elevated [5]. In theory, HLA-matching would be the preferred method to avoid allo-sensitization and hence, (chronic) rejection, and there is some data from retrospective analyses supporting this in lung transplantation [7]. Even in kidney transplantation, however, where higher volumes enable better donor-recipient pairing, HLA-

Abbreviations: AMR, antibody-mediated rejection; BOS, Bronchiolitis obliterans syndrome; CDC, complement-dependent cytotoxicity; CLAD, chronic lung allograft dysfunction; DSA, donor-specific antibody; HLA, human leukocyte antigen; ISHLT, International Society for Heart and Lung Transplantation; IQR, interquartile range; PRA, panel reactive antibody.

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matching is only performed in some regions (e.g. Eurotransplant), and only a certain degree of matching is achievable [8]. While HLA-matching is therefore infeasible in lung transplantation [9], PRA (panel reactive antibody)-positive pre-sensitized recipients are usually only transplanted with crossmatch-negative donor lungs to avoid early antibody-mediated rejection [10].

Yet, how important is the role of HLA pre-sensitization to allo-antigens due to previous lung transplantations? In kidney transplantation, availability of a donor organ for a kidney re-transplantation is scarce since assumed or proven HLA sensitization of the recipient is a defined contraindication for re-transplantation and therefore reduces the likelihood of finding a suitable second organ donor [11,12].

HLA homologies between the first and the second donor are thought to elevate the risk of acute and chronic rejections due to pre-sensitization of the recipient to HLA antigens of the first donor. In kidney transplantation, these so called "unacceptable antigens", which are repeated HLA mismatches as defined by the individual transplant centre, are relevant for the allocation, in some regions and centres irrespective of the existence of corresponding circulating anti-HLA antibodies [13]. The relevance of these repeated HLA mismatches in lung re-transplantation is not known yet.

2. Objective

Here, we present a large cohort of lung re-transplantations performed at Hannover Medical School from 1985 to 2014. We hypothesized that lung re-transplantations across 'unacceptable antigen'-barriers in the absence of donor-specific anti-HLA antibodies have equivalent survival and CLAD-free survival as control re-transplants.

3. Methods

Data from all lung re-transplantations performed at Hannover Medical School between 1985 and 2014 were collected. A retrospective analysis of donor and recipient HLA typing data was performed focussing on HLA homologies between the donors of the first and subsequent transplantations. Clinical data including recipient characteristics such as age, sex, underlying disease, indication for re-transplantation (chronic lung allograft dysfunction, bronchial complications, acute graft failure), time interval between transplantations, survival and CLAD-free survival. Onset of CLAD was defined as the date of first diagnosis of Bronchiolitis Obliterans Syndrome (BOS) grade 1 according to ISHLT consensus criteria [14]. Donor characteristics recorded included age, cause of death and graft ischemic time. HLA data analysis comprised tissue typing of recipients and donors for the HLA-A, HLA-B, HLA-C, HLA-DQ and HLA-DR loci as available. Availability of complete HLA data varied for historical and donor region reasons. HLA-antibodies were detected at our institution by complement-dependent cytotoxicity (CDC) assays until 2006. Starting in 2006, the Luminex multiple antigen bead assay was used routinely for HLA-antibody detection. For further specification, single antigen beads were used if necessary. The infrequent analysis of HLA-Antibodies over the observation period of twenty-nine years does not allow further comparative analysis of this data.

For the purpose of the herein described study, repeated HLA mismatches in the donor for lung re-transplantation were defined as all HLA-alleles of the first donor not matching the HLA-alleles of the recipient. All analyses are based on split-antigens.

PRA before lung re-transplantation and de novo development of donor-specific antibodies (DSA) after lung re-transplantation in the recipient were recorded. Additionally, crossmatch results at the time of re-transplantation were recorded. Routine crossmatching for all lung transplantations were started in 2006. Therefore, crossmatch results for earlier re-transplantations are not systematically available. Starting in 2006, all patients were routinely screened for HLA-antibodies prior to active listing for lung retransplantation. Only in recipients with preformed HLA-antibodies, a warm crossmatch was performed before final acceptance of a donor organ. In recipients without detectable HLA-antibodies, a routine X-match was performed within 24 h after organ transplantation. Routine crossmatching for all lung transplantations was started in 2006. Therefore, crossmatch results for earlier re-transplantations are not systematically available. Given the long time range of this cohort, analyses of DSA were performed using different methods, not sufficiently allowing for quantitative comparison. Therefore, data are reported in a descriptive form.

3.1. Statistical analysis

Demographic characteristics of donors and recipients as well as postoperative parameters were collected and analysed retrospectively. Statistical analyses were performed using GraphPadPrism, Version 5.0, San Diego, CA, USA. Categorical and continuous variables are summarized as percentages, mean ± standard deviation (SD) or median + interquartile range (IQR), respectively. For comparison of continuous variables, standard independent-samples Student's *t*-test was used. Survival was calculated using the Kaplan Meier method and compared by log-rank test. P values <0.05 were considered statistically significant.

4. Results

Between 1985 and 2014, a total of 1858 lung transplantations, including bilateral and single lung as well as combined heart-lung transplantations, were performed at Hannover Medical School. Out of these, a total of 132 lung re-transplantations were identified. 125 patients underwent one lung re-transplantation, six patients received a total of two and one patient of three lung re-transplantations. All re-transplant procedures were summarized and each procedure was considered as one lung re-transplantation event.

The indications for lung re-transplantation comprised chronic lung allograft dysfunction (75.5%, $n = 101$), acute graft failure (12.9%, $n = 17$) and severe bronchial complications (9.8%, $n = 13$). One patient underwent lung re-transplantation for a malignant angiosarcoma of the donor's left atrium, which was diagnosed a few days after transplantation, allowing high urgent re-transplantation (0.8%) (Fig. 1).

In twelve re-transplants, HLA data of either the recipient or the donors were incomplete and therefore not sufficient for analysis. Thus, analysis of HLA data was performed in a total of 120 procedures.

The median age of the recipients at the time of re-transplantation was 36.6 (IQR 27.8–47.9) years. The majority of patients suffered from cystic fibrosis (40.2%) as underlying disease having lead to primary lung transplantation. Other underlying diseases were idiopathic fibrosis (17.4%), emphysema (14.4%), pulmonary hypertension (9.8%) and others (11.4%), including for example sarcoidosis or graft versus host disease.

Onset of CLAD after primary lung transplantation as defined by the first diagnosis of BOS grade 1 occurred in the analysed cohort after a median of 525 (IQR 217–1007) (mean 699.8 ± 647.4) days after primary lung transplantation.

Median time between first and second lung transplantation was 824.5 (IQR 396–1831) days (mean 1175 ± 1143 d). In the cohort of patients receiving a third lung transplantation, median time between second and third transplantation was 1304 (IQR 815–2096) days (mean 1547 ± 916 days). The only patient receiving a fourth lung transplantation at our centre received this 3177 days after the previous transplantation due to CLAD.

4.1. Donor characteristics

Median donor age for lung re-transplantation was 40 (IQR 27–49) years (mean 38 ± 13.6), causes of death were cranial trauma (32.6%), intracranial haemorrhage (28.0%), cerebrovascular stroke (16.7%), hypoxic brain damage (13.6%), others (9.1%). Mean ischemic time of donor