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Casting a smaller net into a bigger donor pool: A single center's experience with the new kidney allocation system

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ABSTRACT

The new kidney allocation system (KAS) provides additional allocation points for candidates with broad HLA sensitization in an effort to increase transplant rates for this underserved population. Following the implementation of KAS, our center lowered the HLA antibody threshold for listing unacceptable antigens from a cytotoxicity crossmatch level to a flow cytometric crossmatch level increasing Calculated Panel Reactive Antibody (CPRA) values and allocation points, yet restricting acceptable donor HLA phenotypes. As a result, many sensitized candidates were transitioned from 50% to 98% CPRA categories into the 99% CPRA regional share and 100% CPRA national share categories. Exposure to these larger donor pools significantly increased transplantation with compatible donors for 100% CPRA candidates, but regional sharing was not sufficient to increase transplantation rates for our 99% CPRA candidates. Competition within the 100% CPRA cohort identified inequities for 99.99–100.0% CPRA candidates and highlighted the continued need for desensitization therapies to reduce immunological barriers and provide transplant opportunities for the most highly sensitized candidates.

1. Introduction

The rollout of the United Network of Organ Sharing (UNOS) kidney allocation system (KAS) in December 2014 has greatly impacted transplantation rates for highly sensitized candidates with high Calculated Panel Reactive Antibody (CPRA) values and, as a result, the practices and protocols used for histocompatibility monitoring of these higher risk candidates [1]. The profile of a highly sensitized or high CPRA candidate can vary widely from a limited set of common HLA antibody specificities to broad sensitization to many HLA class I and class II antigens. Therefore, high CPRA candidates are not equal and some may require a larger donor pool from which to find compatible donors while the route to transplantation for others may require desensitization to remove donor-specific HLA antibody (DSA). Until recently, our center has assigned unacceptable HLA antigens based on positive cytotoxicity crossmatch (CDC-XM) strength HLA antibodies. This non-stringent threshold increased the number of deceased donor offers for our sensitized waitlist candidates, casting a larger net and allowing the transplant team to assess all possible donors for each candidate. This approach included transplanting across DSA barriers and utilized our center's experience with incompatible kidney transplantation and plasmapheresis and intravenous immunoglobulin desensitization protocols [2].

Under the provisions of KAS, additional allocation points are awarded on a sliding CPRA scale and 99% and100% CPRA candidates are eligible for regional and national sharing of organs. Five months following the implementation of KAS, our center's deceased donor transplant rates for high CPRA candidates lagged behind national trends despite our practice of transplanting across DSA barriers. To increase allocation points for our sensitized candidates the threshold for listing unacceptable HLA antigens was lowered to include flow cytometric crossmatch (FC-XM) level HLA antibodies. This increased CPRA values and provided regional and national sharing options to more of our waitlist candidates, but placed a higher restriction on acceptable donor HLA phenotypes.

Abbreviations: DSA, donor-specific HLA antibody; CPRA, Calculated Panel Reactive Antibody; FC-XM, flow cytometric crossmatch; MFI, mean fluorescence intensity; KAS, kidney allocation system.

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Here, we present data highlighting the impact of unacceptable HLA antigen thresholds and the benefits of casting a smaller net into a bigger donor pool.

2. Material and methods

2.1. Study cohort

A retrospective analysis of histocompatibility testing and transplantation data for deceased donor kidney recipients was performed under IRB approval. The threshold to determine transplant eligibility at our center is based on a prospective negative CDC-XM test. Virtual crossmatch assessments to determine DSA presence and cumulative strength are requested at time of donor offers. When multiple DSAs exist, FC-XM tests are performed to confirm virtual crossmatch assessments. Deceased donor kidney transplants were analyzed between 2014 and 2016 during four time periods: 2014 era prior to implementation of KAS allocation (June 1st through November 30th 2014); Early 2015 era post-KAS but prior to optimization of CPRA to include flow cytometric crossmatch level HLA antibodies as unacceptable HLA antigens (January 1st through May 31st 2015); Late 2015 era post-KAS and post-CPRA optimization (June 1st through December 31st 2015); 2016 era also post-KAS and post-CPRA optimization (January 1st through May 23rd 2016).

2.2. HLA typing and unacceptable HLA antigen assignments

Molecular HLA typing was performed by reverse sequence-specific oligonucleotide hybridization (LABType, One Lambda, Canoga Park, CA). HLA antibody testing was performed using Luminex™ phenotype bead panels (Lifecodes Immucor, Stamford, CT) and single antigen panels (LABScreen® Single Antigens, One Lambda, Canoga Park, CA). Hypotonic dialysis of sera was performed to remove interfering factors prior to testing [3]. Unacceptable HLA antigen assignments and CPRA calculations during the 2014 and Early 2015 eras were based on HLA antibody specificities strong enough to yield a positive CDC-XM and CPRA optimization in Late 2015 added flow cytometric crossmatch (FC-XM) level HLA antibody specificities as unacceptable antigens [4]. In general, HLA antibodies were assigned as unacceptable when above a 3000 MFI on a phenotype bead panel and 6000 MFI (HLA-A,B,DR) or 12,000 MFI (HLA-Cw, DQ, DP) using a single antigen bead panel. Additionally, unacceptable antigens may also include antibodies that do not exceed thresholds listed above, but retain their HLA specificity pattern when tested at a 1:8 dilution. HLA antigens representing repeated mismatches with previous allografts may also be listed as unacceptable antigens when requested by the transplant surgeon for some higher risk candidates.

2.3. Flow cytometric and virtual crossmatch assessments

FC-XM tests were performed and acquired on a BD FACSCanto II (BD Bioscience, Franklin Lakes, NJ) using FACSDIVA software (BD Biosciences, Franklin Lakes, NJ, USA) as previously described [5]. All sera were treated using hypotonic dialysis to remove IgM autoantibodies and IgG immune complexes [3]. Thresholds for positivity consist of a ratio of test serum to negative control serum of $\geqslant$2.5 for T and B cells. In rare exceptions, when median channel fluorescence values (MCF) for the negative control serum exceeded the normal range (204 MCF for T cells or 487 MCF for B cells) recipient test serum MFC values of 475 for T cells or 790 for B cells were used as positive thresholds in place of ratios. These latter MFC thresholds have been determined using DSA correlations between solid phase immunoassays and positive/negative FCXM results [4]. Virtual crossmatch assessments were performed to determine the presence of DSA and to predict cumulative DSA levels sufficient to yield positive FC-XMs, as previously described [4]. Assessment of DSA strength involved combined data from phenotype and single antigen bead immunoassays. Individual recipient/donor DSA strength analyses included data from serum dilution studies (1:8 dilution), number of DSA, HLA loci expression levels, and immunodominant and crossreactive HLA antibody specificities [4,6].

2.4. Statistical analyses

Descriptive statistics including mean and standard deviation were determined using Microsoft Excel.

3. Results

3.1. Impact of KAS and CPRA optimization on transplantation rates

Implementation of KAS alone in December 2014 did not increase transplant rates for sensitized candidates with CPRAs $\geqslant$1% at our center (17% 2014 Era versus 13% Early 2015 era, data not shown). However, optimization of CPRA values to including both CDC-XM and FC-XM level HLA antibodies maximized KAS

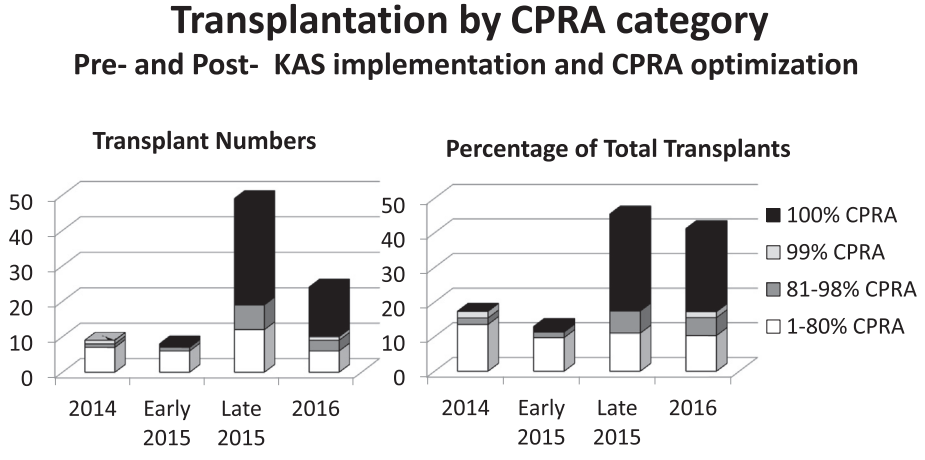

Fig. 1. Transplantation by CPRA category. Bars represent transplant numbers and total transplant percentages for different CPRA categories during the four study time periods. The 2014 era was prior to implementation of KAS allocation; Early 2015 era was post-KAS, but prior to optimization of CPRA to include flow cytometric crossmatch level HLA antibodies as unacceptable HLA antigens; Late 2015 era was post-KAS and post-CPRA optimization; and 2016 era was also post-KAS and post-CPRA optimization.