Use of Bortezomib as Anti-Humoral Therapy in Kidney Transplantation

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INTRODUCTION

The presence of donor-specific anti-human leukocyte antigen antibodies (HLA-DSA) is a critical barrier to successful kidney transplantation (KT). Insufficient reduction or suppression of pre-formed HLA-DSA before KT can result in a hyper-acute or acute antibody mediated rejection (AAMR) (1). In addition, development of HLA-DSA after KT can induce not only acute but also chronic AMR, which could be associated with poor allograft survival (2). For these reasons, research has focused on protocol development to effectively suppress the humoral immune system in kidney transplant recipients (3).

So far, the protocol of plasmapheresis, intravenous immune globulin (PP/IVIG), and rituximab (RTX) has been widely used for desensitization and the treatment of AAMR. This may be because the treatment only depletes B cells or removes circulating antibodies and does not suppress plasma cells that directly produce HLA-DSA (4).

Recently, bortezomib, a proteasome inhibitor, was approved by the Food and Drug Administration for the treatment of multiple myeloma, and has been introduced for use in KT (5). Bortezomib inhibits antibody production from plasma cells, stimulates apoptosis of this cell type, and decreases the number of bone marrow-derived plasma cells (6). Therefore, it is expected that this drug would show stronger suppressive effect for humoral immunity compared with conventional therapies such as rituximab. However, clinical data on the use of bortezomib in KT is currently limited.

Therefore, the aim of this study was to investigate the effect of bortezomib on desensitization before KT and the treatment of AAMR after KT.

MATERIALS AND METHODS

Inclusion criteria and bortezomib protocol

In this study, 9 patients who received bortezomib therapy for desensitization (DSZ group, n = 3) or treatment of AAMR (AAMR group, n = 6) were included. All patients received and did not respond to a conventional treatment composed of RTX and PP/IVIG therapy before use of bortezomib. When the schedules of bortezomib therapy and PP/IVIG put one upon another, bortezomib infused after plasmapheresis.

In the 3 patients of the DSZ group, 2 were highly sensitized to anti-HLA antibody, and 1 was supposed to undergo ABO-incompatible KT and showed extremely high baseline anti-A/B antibody titer (1:1,024). HLA-DSAs were identified using single antigen Luminox bead (Tepnel Lifecodes Corp, Stamford, CT, USA) and reported as MFI. Anti-A/B antibody titer was mea-

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Clinical outcome
AAMR is defined by the Banff 2007 classification (update 2005); biopsies consistent with AAMR required 2 of 3 following characteristics: HLA-DSA, histological findings consistent with AAMR (peritubular capillaritis and glomerulitis), or positive C4d staining in the peritubular capillary and other structures (8). The primary outcome of the AAMR group was the recovery of allograft function (measured as a decrease in serum creatinine or condition that did not require renal replacement therapy). In the DSZ group, success was defined as a negative conversion of the cross match test and MFI score of HLA-DSA < 5,000.

Statistical analysis
Statistical analysis was performed by using SPSS software (version 19.0; SPSS Inc., Chicago, IL, USA). For continuous variables, means were compared using the Student's t-test.

Ethics statement
The study protocol was approved by the institutional review board of Seoul St. Mary's Hospital (IRB No. KC13TNMI0701) and the need for informed consent from the patients was waived because of the retrospective study design.

RESULTS

Baseline characteristics of AAMR group
The demographic and clinical characteristics of the AAMR group (n = 6) are presented in Table 1. There were 2 men and 4 women with a mean age of 41.5 yr (range, 38-46). Two patients underwent deceased and 4 underwent living donor KT. One was a repeat transplantation. One patient showed a positive cross match test (positive T-CDC anti-human globulin augmented method [AHG] and B-CDC tests) and received desensitization therapy with RTX (375 mg/m²) of bortezomib and 375 mg/m² of RTX. Infusion of bortezomib was repeated at the 4th, 8th, and 11th day from the starting date.

Table 1. Baseline characteristics of AMR group

| Pt | Age/Sex | Prior KT | Cause of ESRD | Donor Type | Cross match | ABO incompatible Tx | Kidney Bx (Days, post-Tx) | Bortezomib (Days, post-Tx) | DSA | C4d | PTC |
|----|---------|----------|---------------|------------|-------------|-------------------|--------------------------|--------------------------|-----|-----|-----|
| A  | 43/F    | 0        | DM            | Living     | -           | Compatible        | 7                        | 19                        | +   | +   | +   |
| B  | 46/F    | 0        | CGN           | Living     | +           | Compatible        | 10                       | 12                        | -   | +   | +   |
| C  | 38/M    | 2        | CGN           | Deceased   | -           | -                 | 8                        | 24                        | +   | +   | +   |
| D  | 39/M    | 0        | CGN           | Deceased   | -           | -                 | 4                        | 11                        | +   | +   | +   |
| E  | 32/F    | 0        | Unknown       | Living     | +           | Compatible        | 8                        | 10                        | +   | +   | +   |
| F  | 39/F    | 0        | CGN           | Living     | +           | Incompatible      | 4                        | 11                        | +   | +   | +   |

Pt, patient; KT, kidney transplantation; ESRD, end-stage renal disease; Bx, biopsy; Tx, transplantation; DSA, donor specific antibody; PTC, peritubular capillitis; DM, diabetes mellitus; CGN, chronic glomerulonephritis.
Table 2. Baseline characteristics of two patients with pre-sensitization to anti-HLA antibody

| Parameters                  | Patient G  | Patient H  |
|-----------------------------|------------|------------|
| Sex                         | F          | M          |
| Age (yr)                    | 52         | 56         |
| Prior KT                    | 0          | 2          |
| Cause of ESRD               | Unknown    | CGN        |
| CDC-PRA (class II, %)       | 100/75     | 100/75     |
| Luminex SA                  |            |            |
| MFI max                     | 60/46 (567) | 11/135 (A24) |
| Cross match                 |            |            |
| T-CDC AHG                   | 1:2        | 1:4        |
| B-CDC                       | -          | -          |
| T-Flowcytometry             | +          | +          |
| B-Flowcytometry             | -          | +          |

KC, kidney transplantation; ESRD, end-stage renal disease; CGN, chronic glomerulonephritis; CDC, complement-dependent cytotoxicity; PRA, panel reactive antibody; SA, single antigen; MFI, mean fluorescence intensity; AHG, anti-human globulin.

DISCUSSION

Over the past several years, protocols composed of PP/IVIG and RTX were most widely used in the treatment of AAMR and in pre-transplant desensitization for highly sensitized patients or ABO-mismatch KT. However, this protocol has some limitations: the rate at which reversal of AAMR is achieved is rather gradual than prompt; it costs a great deal; AAMR reversal rates are relatively lower (<80%); chronic rejection may occur after AAMR treatment; and finally, HLA-DSA may persist for a long time after the therapy. These limitations may be due to unsatisfactory effects on mature plasma cells (5).

Our experience with bortezomib was applied in the following situations: treatment of AAMR and desensitization for anti-HLA or anti-ABO antibody before KT. Out of 6 AAMR treatment cases (the patients A-F), 3 patients experienced a full recovery from AAMR after bortezomib treatment. Serum creatinine levels recovered to baseline and HLA-DSA decreased to a weak or negative level. In the patients C, D and E, allograft function did

Previously, the best result was achieved when serum creatinine levels decreased to less than the target (≤1:16), resulting in successful transplantation.
not improve even after 4 bortezomib infusions, and maintenance hemodialysis was required. Additionally, HLA-DSA of those patients did not decrease. The factors associated with response to bortezomib therapy have not been established. In previous reports (5, 9), only 1 study described bortezomib efficiency in early AMR with a relatively preserved renal function and low proteinuria (10). In this study, however, successful response was found in cases of first transplantation from a living donor. However, further investigation on bortezomib therapy in treatment of AAMR, conducted on a larger patient group, is required.

In our study, desensitization in 2 highly sensitized patients (the patient G and H) and 1 ABO mismatch KT with extremely high baseline anti-A/B antibody titer was successful. Until the present, a desensitization protocol using bortezomib has not been established. Previous studies suggested that HLA-DSA reduction can be achieved with bortezomib alone (5), but another recommend to use additional extracorporeal therapy with bortezomib (11). In this study, we decided to include RTX/PP/IVIG in our bortezomib protocol, and desensitization of HLA antibody or ABO antibody was successful in all cases. However, further investigation may be required to disseminate an effective desensitization protocol using bortezomib.

In previous reports, various side effects of bortezomib have been reported. The most common complaints of bortezomib use were fatigue and lethargy (45%) (10). Anemia (20%-26%), thrombocytopenia (25%-35%) and neutropenia (19%-20%) were also relatively common. Other toxicities in KT occurred at similar or lower frequencies to the multiple myeloma population (12). We did not experience any serious complications with bortezomib use (10), and only mild thrombocytopenia and lethargy were reported due to boetrzomib (12). In addition, it is unclear whether the main cause of those side effects was bortezomib or the concomitant therapies (RTX, PP/IVIG, steroid, or ATG). As a result, the use of bortezomib was generally well tolerated in most patients.

This study has some limitations. It includes a small number of patients with less than 1 yr of follow up in desensitization. Further investigation conducted on a larger patient group with a longer follow-up time may be required to elucidate its safety and efficacy as an anti-humoral therapy.

In conclusion, bortezomib could be considered as an alternative therapeutic option for desensitization and treatment of AAMR in cases that do not respond to conventional therapies such as RTX/PP/IVIG.

**DISCLOSURE**

The authors have declared that no conflict of interest exists.

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