Renal transplantation across the donor-specific antibody barrier: Graft outcome and cancer risk after desensitization therapy

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KEYWORDS
desensitization; kidney transplantation; urothelial carcinoma

Background/Purpose: Desensitization regimens including use of intravenous immune globulin and rituximab have been reported to overcome renal transplant hyperacute rejection. A retrospective case-control study was performed to assess the results and complications of renal transplantation with desensitization therapy for donor-specific antibody (DSA) in a transplant center in Asia, where donor exchange was usually not allowed.

Methods: Between January 2007 and December 2013, 22 patients with DSA received live-donor renal transplantation after desensitization (DSA group). During the same period, the DSA group was compared to the NSA group (152 renal transplants) who had no specific antibody to the donors (66 from deceased donors and 86 from living relatives). Rejection, renal function, graft and patient survival rates, infection, and cancer incidence were reviewed and analyzed from medical records.

Results: The DSA group (46.8%) had significantly higher acute rejection rates than the NSA group (13.7%) at the 1-year follow-up. The estimated renal function, 5-year graft, and patient survival rates were comparable between the groups. The DSA group (19.6%) had significantly higher 5-year de novo cancer incidence than the NSA group (8.5%; \( p = 0.028 \)); three patients of the DSA group developed urothelial carcinoma 17.0 ± 3.0 months after transplantation. By using stepwise Cox regression analysis, desensitization therapy was identified as the sole independent risk factor for post-transplant urothelial carcinoma.
Introduction

Donor-specific antibody (DSA) against human leukocyte antigens (HLA) has been recognized as one of the most important obstacles to successful renal transplantation. Renal transplantation with DSA could lead to hyperacute rejection or early antibody-mediated rejection (AMR) and result in premature transplant failure.1,2 During the past 10 years, the development of desensitization protocols has explored the possibility of renal transplantation across DSA and has demonstrated encouraging short-term outcomes in highly-sensitized transplant candidates.3

Desensitization regimens including use of intravenous immune globulin and rituximab have been shown to overcome DSA and AMR. In 2003, Jordan et al4 reported that an intravenous immunoglobulin (IVIG) treatment could inhibit crossmatch positivity and allow for successful transplantation. In addition, Gloor et al5 developed a desensitization regimen, including pretransplant plasmapheresis, IVIG, rituximab, and splenectomy to overcome live donor kidney transplantation with positive crossmatches. However, chronic AMR after renal transplantation remains a serious concern, and the risk of infectious and neoplastic complications after desensitization, such as polyoma BK virus-associated nephropathy and urothelial carcinoma, need to be properly addressed.6–8

With the success of ABO-incompatible renal transplantation following rituximab use instead of splenectomy, our transplant center developed a desensitization protocol for live donor renal transplantation with DSA in 2007 that includes plasmapheresis, IVIG, and rituximab.9,10 In this study, we aimed to present information on graft outcomes and complications after renal transplantation across DSA from our transplant center in Asia, where paired exchange was usually not permitted.

Methods

Study design

Between January 2007 and December 2013, a total of 331 renal transplants were performed at our transplant center. With the exclusion of ABO incompatible, HLA zero-mismatched, pediatric, or multiorgan transplants, a total of 174 ABO-compatible but HLA-mismatched adult renal transplants, including 66 from deceased donors and 108 from live donors, were reviewed for transplant outcomes. Of the 108 live donor renal transplant recipients, 22 were positive for DSA and received desensitization therapy prior to transplantation. Outcomes of the desensitization therapy were compared between those who underwent renal transplantation with DSA (DSA group, n = 22) and those with nonspecific antibody to the donors (NSA group, n = 152). The NSA group included 86 patients receiving renal transplants from live donors (L-NSA subgroup) and 66 from deceased donors (D-NSA subgroup).

Pretransplant antibody screening

Patients eligible for live donor transplantation or waiting on the transplant list were checked for HLA antibody regularly by flow cytometry panel-reactive antibody (PRA) tests, and conventional complement-dependent cytotoxicity (CDC) tests were performed in all cases before renal transplantation. For patients with high levels (> 50%) of preformed PRA or positive CDC, One Lambda LabScreen Single Antigen tests were used to detect possible DSA. DSA positivity was defined as any HLA antibody (> 1000 mean fluorescence intensity (MFI)), targeting the unacceptable donor antigens as assigned by the single antigen assays.

Desensitization and criteria for transplantation

Before live-donor renal transplantation, patients who were positive for DSA received desensitization therapy, which was modified from our protocol for ABO-incompatible renal transplantation.9 In brief, our desensitization therapy for DSA includes two doses of rituximab, one dose of 200 mg for approximately 14 days before transplantation, and the other during the transplant operation, at least four sessions of double filtration plasmapheresis (DFPP) and IVIG (2 g/kg in total) were performed. DFPP was accomplished, as described previously, using a KM-8800 in a Kuraray plasmapheresis system incorporating a Plasmacure PS-06 and an Evaflux 4A as the plasma fractionator (Kuraray Medical, Tokyo, Japan).11 Renal transplantation would then be performed when the T-cell CDC against the prospect donor became negative and the desensitization therapy was completed. Of note, B-cell CDC was always intensely positive after rituximab therapy. For patients who were CDC-positive even after completion of the desensitization therapy, DFPP and IVIG (0.5 g/kg after every DFPP) sessions were performed again every other day until the CDC test became negative for T cells. Desensitization therapy would be considered as a failure (2 cases in this study) and the transplantation was cancelled when the T-cell CDC was still positive after a total of eight sessions of DFPP and 4 g/kg of IVIG.

Immunosuppressive therapy and infection prophylaxis

In addition to the desensitization therapy, patients with DSA (the DSA group) were administered preconditioning
immunosuppressive therapy since the day when desensitization therapy started. The preconditioning therapy was basically a tacrolimus-based regimen, including tacrolimus combined with mycophenolate mofetil and intravenous methylprednisolone. The NSA group did not receive antibody induction, but tacrolimus-based immunosuppression was initiated after transplantation. The initial target trough levels for tacrolimus were 8–16 ng/mL, and mycophenolate mofetil was prescribed at an initial dose of 1–2 g/d. White blood cell counts were maintained between 4.0 \times 10^9/L and 6.0 \times 10^9/L, unless intolerance occurred or the maximum dose was reached. Corticosteroids, including intravenous methylprednisolone and oral prednisolone, were given according to standard practices. The dose of prednisolone was reduced to 2.5–5 mg/d at 12 months and could then be discontinued if significant side effects were reported. To prevent cytomegalovirus (CMV) infection after transplantation, valganciclovir (450 mg/d) was administered to patients with or without anti-CMV-IgG for 3 months or 12 months, respectively.

**Biopsy and acute rejection**

Graft renal biopsy was conducted when allograft rejection or dysfunction, as defined by elevation of serum creatinine > 20%, significant proteinuria (1 g/d), or unsatisfactory graft function (persistent edema or serum creatinine > 2 mg/dL), was suspected. Protocol biopsy was performed annually unless the patient refused or an event-based biopsy had been executed in the past 6 months. Pathological diagnosis of rejection was made based on Banff criteria at the time of biopsy. Acute rejection episodes (either C4d⁺ or not) were treated with a 3-day methylprednisolone (10 mg/kg) pulse therapy. Patients with antibody-mediated rejection received additional desensitization therapy after transplantation including four sessions of DFPP and IVIG (0.5 g/kg after every session of DFPP).

**Statistical analysis**

Continuous variables are presented as mean ± standard deviation. Unpaired two-tailed t tests and Fisher’s exact tests were used for normally distributed continuous variables and categorical variables, respectively. Donor and recipient renal function (persistent edema or serum creatinine > 2 mg/dL), was suspected. Protocol biopsy was performed annually unless the patient refused or an event-based biopsy had been executed in the past 6 months. Pathological diagnosis of rejection was made based on Banff criteria at the time of biopsy. Acute rejection episodes (either C4d⁺ or not) were treated with a 3-day methylprednisolone (10 mg/kg/d) pulse therapy. Patients with antibody-mediated rejection received additional desensitization therapy after transplantation including four sessions of DFPP and IVIG (0.5 g/kg after every session of DFPP).

**Results**

**Patient characteristics**

Patient demographics of the DSA and NSA groups, including L-NSA and D-NSA subgroups, are summarized in Table 1. The mean age of the DSA group at transplantation (46.9 ± 9.0 years) was significantly older than that of the NSA group (41.7 ± 13.0 years, p = 0.023). When comparing subgroups, the mean age of the DSA group was comparable to that of the D-NSA subgroup (46.0 ± 10.1, p = 0.709) but was significantly higher than that of the L-NSA subgroup (38.4 ± 14.0, p = 0.008), probably because of a significantly higher number of second transplants in the DSA group (8/22, 36.4%) than in the NSA group (4/152, 2.6%). There were significantly more female patients in the DSA group (77.3%, 17/22) than in the NSA group (44.1%, 67/152; p = 0.005), and the difference remained statistically significant when comparisons were made between the two subgroups (p = 0.003 for the L-NSA subgroup and p = 0.025 for the D-NSA).

The distribution of sexes of the donors was not significantly different between the DSA and NSA groups, although there seemed to be more male donors in the D-NSA subgroup than in the L-NSA subgroup. The mean donor age of the DSA group (50.2 ± 12.3) was significantly higher than that of the NSA group (44.0 ± 11.8; p = 0.035), mainly because of the high number of young donors in the D-NSA subgroup (p = 0.003). However, the eGFRs of the donors were comparable between the two groups of patients including the subgroups. The DSA group had significantly more HLA mismatches (3.2 ± 1.4) than the NSA group (2.61 ± 1.1), especially in the D-NSA subgroup (2.5 ± 1.1). In addition, the DSA group had significantly higher PRA class I (71.7 ± 31.9 vs. 8.4 ± 19.6) as well as PRA class II (63.8 ± 38.0 vs. 7.5 ± 19.0) than the NSA group. Actually, the DSA group (21/22, 95.5%) included a significantly higher percentage of patients with experience of blood transfusion when compared to the NSA group (92/152, 60.5%).

**Donor-specific antibody and acute rejection**

After evaluation and desensitization, none of the patients in either group presented episodes of hyperacute rejection, although 16 patients in the DSA group were positive for CDC before desensitization. Of the 22 patients in the DSA group, 19 were positive for HLA class I DSA, but only nine were positive for class II. The average MFIs of the DSA group were 4111 ± 4766 (range, 1416–21,751) for the highest HLA class I DSA and 9473 ± 11,418 (range, 1605–41,118) for the highest class II DSA. Patients with a strong DSA (MFI > 10,000) had a 100% rejection rate at 1 month, and the rejection rates of those with intermediate DSA (MFI 5000–10,000) and low DSA (MFI 1000–5000) were 40% and 15.4%, respectively. The DSA levels were statistically significant for acute rejection of the DSA group after desensitization (p = 0.027).

When compared to the NSA group, patients with DSA had a significantly higher 1-year acute rejection rate even after desensitization (46.8% vs. 13.7%, p < 0.001; Figure1). Interestingly, the 1-year incidence of AMR was not as high
As expected in the DSA group (27.3%), but it was still higher than that of the NSA group (5.3%, \( p < 0.003 \)). As for chronic AMR after more than 6 months, three patients in the DSA group (3/22, 13.6%), six in the NSA group (6/152, 3.9%), one in the L-NSA subgroup, and five in the D-NSA subgroup, had chronic AMR during the follow-ups; the incidence of chronic AMR between the DSA and NSA groups did not reach statistical significance. However, when compared to the L-NSA subgroup, the DSA group had a significantly higher risk of chronic AMR (\( p < 0.026 \)). Moreover, the average eGFRs of the DSA group were not significantly different from those of the NSA group 4 years after transplantation, although in the NSA group, the L-NSA subgroup had significantly (\( p < 0.05 \)) better eGFRs than the D-NSA subgroup at 12 months, 24 months, 36 months, and 42 months post-transplant (Figure 2). The DSA group seemed to have comparable eGFRs to the L-NSA subgroup in the first year, but the eGFR of the DSA group dropped and fluctuated between the levels of those in the L-NSA and D-NSA, possibly because of acute rejection and anti-rejection treatments. The overall outcomes of the two groups are summarized in Table 2.

### Infections and complications

The 5-year graft and patient survival rates between the DSA and NSA groups, as well as the subgroups, were comparable. One patient from the DSA group had *Pneumocystis jiroveci* pneumonia and another had bacterial pneumonia. All patients in the DSA group are currently surviving, but two grafts failed because of chronic rejection. As for the NSA group, three patients with polyoma BK virus-associated nephropathy, two with CMV pneumonitis, one with *Pneumocystis jiroveci* pneumonia, and another with tuberculosis were observed. Five patients of the NSA group died with functional renal allografts because of cardiovascular events (\( n = 2 \) patients), acute pancreatitis (\( n = 1 \)), pneumonia of unknown pathogen (\( n = 1 \)), and advanced urothelial carcinoma (\( n = 1 \)). However, three of the 22 patients in the DSA group developed malignancies during a mean follow-up of 51.4 ± 24.4 months, compared with six of the 152 patients

### Table 1  Patient demographics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>NSA (n = 152)</th>
<th>DSA (n = 22)</th>
<th>( p)-value* (vs DSA)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>L-NSA (n = 86)</td>
<td>D-NSA (n = 66)</td>
<td>NSA</td>
</tr>
<tr>
<td>Age at transplantation [years]</td>
<td>41.7 \pm 13.0</td>
<td>46.9 \pm 9.0</td>
<td>0.023</td>
</tr>
<tr>
<td>Gender [M:F]</td>
<td>85:67</td>
<td>5:17</td>
<td>0.005</td>
</tr>
<tr>
<td>Donor age [years]</td>
<td>44.0 \pm 11.8</td>
<td>50.2 \pm 12.3</td>
<td>0.035</td>
</tr>
<tr>
<td>Donor gender [M:F]</td>
<td>75:77</td>
<td>11:11</td>
<td>1.000</td>
</tr>
<tr>
<td>Donor MDRD GFR [mL/min]</td>
<td>100.9 \pm 47.8</td>
<td>92.1 \pm 22.7</td>
<td>0.398</td>
</tr>
<tr>
<td>Blood transfusion history, n (%)</td>
<td>92 (60.5%)</td>
<td>21 (95.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Flow PRA I [%]</td>
<td>8.4 \pm 19.6</td>
<td>3.3 \pm 14.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Flow PRA II [%]</td>
<td>7.5 \pm 19.0</td>
<td>3.4 \pm 11.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Re-transplantation (%)</td>
<td>4 (2.6%)</td>
<td>8 (36.4%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Two-tailed Fisher’s exact test was used for categorical variables; two-tailed unpaired \( t \) test was used for continuous variables.

### Figure 1  Kaplan–Meier estimates of the rejection-free survival rates of the donor-specific antibody (DSA) group, the live donor subgroup (L-NSA), and diseased donor subgroup (D-NSA) subgroup.
in the NSA group over 55.7 ± 24.3 months. In the DSA group, the incidence of post-transplant cancer was 19.6% at 5 years, compared with 8.5% in the NSA group (Figure 3). The difference in post-transplant cancer incidence between the two groups was statistically significant ($p < 0.028$).

Urothelial carcinoma accounted for 100% (3/3) of the pathological diagnoses in the DSA and 50.0% (3/6) of the NSA groups. However, the three patients in the DSA group were found to have urothelial carcinoma in the bladder for two and left kidney for one at 17.0 ± 3.0 months after transplantation as well as three patients in the NSA group (2 in the bladder only and 1 in bilateral kidneys, ureters, and bladder) at 47.3 ± 13.6 months. The remaining three patients of the NSA group developed cancer of the endometrium, colon, or thyroid at 58 months, 33 months, and 26 months, respectively. Interestingly, eight of the nine patients with post-transplant cancer in this study were female. Neither skin cancer nor post-transplant lymphoproliferative disease was detected in any of the patients. As urothelial carcinoma was the major concern of post-transplant malignancies in the DSA group, we performed univariate and stepwise regression analyses to identify the independent risk factors for post-transplant urothelial carcinoma. We found that age at transplantation, donor sex, donor age, acute rejection, AMR, HLA mismatch, and retransplantation were not significantly associated with the

![Figure 2](image-url) **Figure 2** Modification of diet in renal disease estimated glomerular filtration rates of the donor-specific antibody (DSA) group, the live donor subgroup (L-NSA), and diseased donor subgroup (D-NSA) subgroup. The L-NSA subgroup had significantly better eGFRs than the D-NSA subgroup at 12 months, 24 months, 36 months, and 42 months post-transplant. *$p < 0.05$.

![Figure 3](image-url) **Figure 3** Kaplan–Meier estimates of the cumulative cancer incidences of the donor-specific antibody (DSA) group and the live donor subgroup (L-NSA) and diseased donor subgroup (D-NSA) subgroup.

### Table 2  Outcomes of renal transplantation with or without DSA.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>L-NSA (n = 152)</th>
<th>D-NSA (n = 22)</th>
<th>D-NSA (n = 66)</th>
<th>P-value* (vs DSA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-yr acute rejection</td>
<td>13.7%</td>
<td>46.8%</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1-yr antibody-mediated rejection</td>
<td>9.5%</td>
<td>19.5%</td>
<td>0.003</td>
<td>0.013</td>
</tr>
<tr>
<td>Chronic AMR after 6 months, n (%)</td>
<td>6 (3.9%)</td>
<td>3 (13.6%)</td>
<td>0.089</td>
<td>0.388</td>
</tr>
<tr>
<td>1-yr MDRD GFR [mL/min]</td>
<td>58.0 ± 22.7</td>
<td>61.2 ± 13.4</td>
<td>0.543</td>
<td></td>
</tr>
<tr>
<td>5-yr patient survival</td>
<td>96.3%</td>
<td>100.0%</td>
<td>0.416</td>
<td></td>
</tr>
<tr>
<td>5-yr cancer incidence</td>
<td>8.5%</td>
<td>19.6%</td>
<td>0.028</td>
<td></td>
</tr>
<tr>
<td>Follow-up [months]</td>
<td>55.7 ± 24.3</td>
<td>51.4 ± 24.4</td>
<td>0.444</td>
<td></td>
</tr>
</tbody>
</table>

AMR, antibody-mediated rejection; MDRD, modification of diet in renal disease (equation); GFR, glomerular filtration rate. *Log-rank test was used for survival analysis; two-tailed unpaired t test was used for continuous variables.
While bortezomib, a proteasome inhibitor that had previously increased the rejection rate of the DSA group was still relatively high (90%) and similar to those without DSA, even though the 1-year acute DSA, in our experience, seemed acceptable (> 90%) and similar to those without DSA, even though the 1-year acute rejection rate of the DSA group was still relatively high (90%) and similar to those without DSA, even though the 1-year acute DSA, in our experience, seemed acceptable (> 90%) and similar to those without DSA, even though the 1-year acute DSA, in our experience, seemed acceptable (> 90%) and similar to those without DSA, even though the 1-year acute DSA, in our experience, seemed acceptable (> 90%) and similar to those without DSA, even though the 1-year acute DSA, in our experience, seemed acceptable (> 90%) and similar to those without DSA, even though the 1-year acute DSA, in our experience, seemed acceptable (> 90%) and similar to those without DSA, even though the 1-year acute DSA, in our experience, seemed acceptable (> 90%) and similar to those without DSA, even though the 1-year acute DSA, in our experience, seemed acceptable (> 90%) and similar to those without DSA, even though the 1-year acute DSA, in our experience, seemed acceptable (> 90%) and similar to those without DSA, even though the 1-year acute DSA, in our experience, seemed acceptable (> 90%) and similar to those without DSA, even though the 1-year acute DSA, in our experience, seemed acceptable (> 90%) and similar to those without DSA, even though the 1-year acute DSA, in our experience, seemed acceptable (> 90%) and similar to those without DSA, even though the 1-year acute DSA, in our experience, seemed acceptable (> 90%) and similar to those without DSA, even though the 1-year acute DSA, in our experience, seemed acceptable (> 90%) and similar to those without DSA, even though the 1-year acute DSA, in our experience, seemed acceptable (> 90%) and similar to those without DSA, even though the 1-year acute DSA, in our experience, seemed acceptable (> 90%) and similar to those without DSA, even though the 1-year acute DSA, in our experience, seemed acceptable (> 90%) and similar to those without DSA, even though the 1-year acute DSA, in our experience, seemed acceptable (> 90%) and similar to those without DSA, even though the 1-year acute DSA, in our experience, seemed acceptable (> 90%) and similar to those without DSA, even though the 1-year acute DSA, in our experience, seemed acceptable (> 90%) and similar to those without DSA, even though the 1-year acute DSA, in our experience, seemed acceptable (> 90%) and similar to those without DSA, even though the 1-year acute DSA, in our experience, seemed acceptable (> 90%) and similar to those without DSA, even though the 1-year acute DSA, in our experience, seemed acceptable (> 90%) and similar to those without DSA, even though the 1-year acute DSA, in our experience, seemed acceptable (> 90%) and similar to those without DSA, even though the 1-year acute DSA, in our experience, seemed acceptable (> 90%) and similar to those without DSA, even though the 1-year acute DSA, in our experience, seemed acceptable (> 90%) and similar to those without DSA, even though the 1-year acute DSA, in our experience, seemed acceptable (> 90%) and similar to those without DSA, even though the 1-year acute DSA, in our experience, seemed acceptable (> 90%) and similar to those without DSA, even though the 1-year acute DSA, in our experience, seemed acceptable (> 90%) and similar to those without DSA, even though the 1-year acute DSA, in our experience, seemed acceptable (> 90%) and similar to those without DSA, even though the 1-year acute DSA, in our experience, seemed acceptable (> 90%) and similar to those without DSA, even though the 1-year acute DSA, in our experience, seemed acceptable (> 90%) and similar to those without DSA, even though the 1-year acute DSA, in our experience, seemed acceptable (> 90%) and similar to those without DSA, even though the 1-year acute DSA, in our experience, seemed acceptable (> 90%) and similar to those without DSA, even though the 1-year acute DSA, in our experience, seemed acceptable (> 90%) and similar to those without DSA, even though the 1-year acute DSA, in our experience, seemed acceptable (> 90%) and similar to those without DSA, even though the 1-year acute DSA, in our experience, seemed acceptable (> 90%) and similar to those without DSA, even though the 1-year acute DSA, in our experience, seemed acceptable (> 90%) and similar to those without DSA, even though the 1-year acute rejection rate of the DSA group was controlled at a lower incidence (13.6%), who did not include IVIG in their desensitization regimen. The 5-year graft survival rate of renal transplantation with a CNI-based immunosuppression was reported to increase the risk of urothelial carcinoma after transplantation at a risk ratio of 7.81 (p = 0.010; Table 4).

### Discussion

With desensitization protocols including the use of rituximab and IVIG, outcomes of DSA-positive renal transplantation have been encouraging, although the incidences of AMR remain around 30%. While nonmelanoma skin cancer and lymphoproliferative disorders are prevalent in Western countries, urothelial carcinoma is very common among Asian renal transplant patients. Chinese herbal medications containing aristolochic acid could contribute to the higher incidence of urothelial carcinoma in Asian patients. While nonmelanoma skin cancer and lymphoproliferative disorders are prevalent in Western countries, urothelial carcinoma is very common among Asian renal transplant patients. Chinese herbal medications containing aristolochic acid could contribute to the higher incidence of urothelial carcinoma in Asian patients.

Immunosuppressive therapy has played an important role in the occurrence of post-transplant cancers in renal transplant patients. The incidence of malignancies, as showed, was higher in patients treated with a calcineurin inhibitor (CNI). Furthermore, induction therapy with a T-cell-depletive biological agent has also been reported to be associated with post-transplant cancer, mostly skin cancer and urothelial cancer. Receiving an even stronger immunosuppressive therapy—including rituximab, preconditioning immunosuppression, and more antirejection therapy—than just induction and a CNI-based regimen, patients with DSA would require careful surveillance for detection of malignancies after desensitization and transplantation. Actions should be taken to prevent post-transplant cancer especially in highly sensitized patients who undergo desensitization therapy. Previously, macrocyclic lactone inhibitors of the mammalian target of polyoma BK viremia and associated nephropathy. Fortunately, we did not encounter any case of BK nephropathy in the DSA group, and all of the allografts survived DSA with the exception of two with chronic AMR. Nevertheless, the increased acute rejection rate and comparable graft survival rates of our DSA group suggested that the potent and sustained immunosuppressive therapy given controlled the rejection responses. Our DSA group had a significantly higher incidence of post-transplant urothelial carcinoma during the follow-up periods, although cancer risk of the ABO-incompatible renal transplantation did not increase. Three female patients from the DSA group had urothelial carcinoma at 17.0 ± 3.0 months post-transplantation. De novo malignancy, especially urothelial carcinoma, after desensitization could be a grave threat to highly sensitized renal transplant patients in Asia, although many factors other than desensitization have been reported to increase the risk of urothelial carcinoma.

### Table 3: Univariate analyses of risk factors for urothelial carcinoma.

<table>
<thead>
<tr>
<th>Log-rank test</th>
<th>Category</th>
<th>No. of patients</th>
<th>5-y incidence of urothelial carcinoma (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desensitization</td>
<td>Yes</td>
<td>22</td>
<td>19.6</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>152</td>
<td>4.6</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>85</td>
<td>12.7</td>
<td>0.012</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>89</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

### Table 4: The final model of stepwise Cox regression analysis of the factors with statistical significance in the univariate analyses.

<table>
<thead>
<tr>
<th>Cox regression</th>
<th>Regression coefficient</th>
<th>Standard error</th>
<th>Risk ratio</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desensitization</td>
<td>2.11</td>
<td>0.82</td>
<td>7.81</td>
<td>0.51</td>
<td>3.72</td>
<td>0.010</td>
</tr>
</tbody>
</table>

CI = confidence interval.
rapamycin signaling pathway, such as sirolimus or everolimus, were shown to exert both anticancer and immunosuppressive effects.\textsuperscript{29} We recently reported that de novo therapy with low-dose sirolimus combined with a CNI could possibly reduce the risk of post-transplant cancer in renal transplant recipients.\textsuperscript{30} The higher risk of post-transplant cancers warrants long-term studies on the effects of mammalian target of rapamycin inhibitors in the prevention of cancers after desensitization for DSA.

In conclusion, to overcome complications due to DSA, desensitization therapy using rituximab and IVIG resulted in equivalent renal transplant survival rates and function, but risk of urothelial carcinoma could be higher after renal transplantation, when compared with those without DSA and the desensitization therapy.

Acknowledgments

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