BK Viral Infection and Malignancy in Renal Transplantation
~A Case History~

Mariko Toyoda, MD

Department of Nephrology,
Japanese Red Cross Kumamoto Hospital
Statement of Disclosure

The author does not have any financial conflict of interests regarding the material in this presentation.
Case

Patient: 67 year-old female (at transplant)
Original Kidney Disease: Nephrotuberculosis
Past History: Rt Pyogenic arthritis of the hip
Family History: No Kidney Disease
Blood Transfusion History: Yes
Reproductive History: 3 pregnancies
Present Illness

- At 19, she presented with pulmonary tuberculosis and at 20, nephrotuberculosis was determined. Due to right nephrectomy and left ureter stenosis, her kidney function was decreased.
- At 56, hemodialysis was initiated.
- At 66, she consulted our hospital about a living-donor kidney transplantation from her spouse.
Status Before Kidney Transplantation (KT)

Status

Height: 152cm  Weight: 46kg  BMI: 20
Blood Pressure: 137/86 mm Hg  HR: 86 /min
Heart: No murmur  Lung: No rale
Abdomen: Soft and flat
Leg edema: None

Medications

Esomeprazol, Rebapimide, Cinacalcet,
Sevelamer Hydrochloride, Precipitated Calcium Carbonate,
Candesartan Cilexetil
Donor Details

• Spouse (67 year-old male)
• Blood Type: B
• Past History: Cholecystectomy (Gallstones)
• Medication: None
• Kidney Function: Normal
Serologic Tests for Screening of Infectious Diseases Before KT

- HBsAg(-), HBsAb(-), HBcAb(-), HCV Ab(-)
- HIV Ab(-), HTLV-1 Ab(-)
- HSV IgG(+), VZV IgG(+), CMV IgG(+), Rubella IgG(+), Measles IgG(+), Mumps IgG(+)
- EBNA-IgG(+), EB-VCA AgG(+)
- TB IFNγ(TSPOT) (-)
Immunological Examinations Before KT

Blood Type: B→O

HLA Type:
  Recipient A(24.35) B(61.14) DR(15.-)
  Donor A(24.-) B(51.54) DR(9.13)

X-Match:
  • LCT: T(-)B(-)
  • FCXM: T(-)B(-)
  • PRA: Class1(-), Class2(-)
Imaging Studies Before KT

- Chest X-Ray
- Ecocardiogram
- Echo Cardiography
- Whole Body CT
- Abdominal Ultrasound
- Colorectal Endoscopy

No significant findings on any of these studies.
Gastric Endoscopy

The gastric endoscopy showed early gastric cancer. (Stage 1A).
Problem Before KT

Gastric Cancer (Early Stage)

How should we prepare for her renal transplantation?
ESD indication

1) Differentiated adenocarcinoma
2) Intramucosal cancer (Stage 1A)
3) Size of the lesion less than 20 mm,
4) Without any endoscopic findings of ulceration
5) No LN involvement or metastasis by computed tomography

Curative resection

1) Differentiated adenocarcinoma
2) Intramucosal cancer (Stage 1A)
3) Size of the lesion less than 20 mm,
4) Without ulceration
5) No lymph duct and vascular invasion
6) Negative surgical margins
## Recommended Cancer-Free Periods

<table>
<thead>
<tr>
<th>Organ</th>
<th>Tumor Type</th>
<th>Minimal Wait Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>Wilms Tumor</td>
<td>2 years</td>
</tr>
<tr>
<td></td>
<td>Renal Cell Carcinoma</td>
<td>2 years (&lt;5cm)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 years (&gt;5cm)</td>
</tr>
<tr>
<td>Bladder</td>
<td>In Situ</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Invasive</td>
<td>2 years</td>
</tr>
<tr>
<td>Prostate</td>
<td></td>
<td>2 years</td>
</tr>
<tr>
<td>Uterus</td>
<td>Cervix (In Situ)</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Cervical Invasive</td>
<td>2-5 years</td>
</tr>
<tr>
<td></td>
<td>Uterine Body</td>
<td>2 years</td>
</tr>
<tr>
<td>Breast</td>
<td></td>
<td>2-5 years</td>
</tr>
<tr>
<td>Colorectal</td>
<td></td>
<td>2-5 years</td>
</tr>
<tr>
<td>Lymphoma</td>
<td></td>
<td>2-5 years</td>
</tr>
<tr>
<td>Skin (Local)</td>
<td>Basal Cell</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Squamous Cell</td>
<td>Surveillance</td>
</tr>
<tr>
<td></td>
<td>Melanoma</td>
<td>5 years</td>
</tr>
</tbody>
</table>

Handbook of Kidney Transplantation 5th edition
Clinical Course

Endoscopic Submucosal Dissection (ESD) was performed 3M prior to KT.

The cancer lesion was excised completely.
Immunosuppressive Regimen
for ABO Incompatible & HLA-DSA Positive

- **Transplant**
  - **Rituximab** 200mg/body
  - **Mycophenol Mofetil**
    - 1000mg/Day
    - 3000mg/Day with CsA
    - 2500mg/Day with TAC
  - **CsA or TAC**
  - **Target AUC_{0-4h}**; CsA 3500, TAC 80 ng·hr/ml

- **Basiliximab** 20mg D.I.V.
- **Prednisolone**
- **Sarpogrelate Hydrochlorides (Unplaque 300mg/3x)**

- **Starting Dose**:
  - CsA 4mg/kg, TAC 0.1mg/kg po BID

- **DFPP**
- **PEX**
- **Discharge**
Clinical Course

Plasma BKV-DNA (10^4 Copies/ml)

Cr (mg/dl)

* Tacrolimus
  - Trough 5-6ng/ml
  - Trough 4-5ng/ml
  - Trough 2-3ng/ml

Prednisolone
- 10mg
- 5mg

MMF
- 1.5g
- 1.0g
- 0.75g
- 0.5g

Clinical Course

Month

Decoy Cell
- + + + - + + + +

Biopsy

* prolonged release Tacrolimus
Kidney Biopsy

A

B

C

D

H&E stain

H&E stain × 400

SV40
Clinical Course

Cr (mg/dl)

Plasma BKV-PCR (10^4 Copies/ml)

*Tacrolimus
Trough 5-6ng/ml
Trough 4-5ng/ml
Trough 2-3ng/ml

Prednisolone

MMF
1.5g
1.0g

1.5g
1.0g
0.75g
0.5g

EVR Trough 5-6ng/ml

Biopsy

Decoy Cell

+ + + + + + +

* prolonged release Tacrolimus
How to screen for BKV infection?

1. Decoy Cells (Urine)
2. PCR (Plasma)
3. Allograft Function
4. Allograft Biopsy (Protocol)
Screening and Treating BKV Replication and Disease

1. Urine cytology for decoy cell/PCR
   If a positive test result, we should perform PCR in plasma

2. PCR for BKV DNA in plasma
   BKV DNA loads of >4log 10 cp/ml shows high specificity in diagnosis of BKV nephropathy.

Monthly for the first 3–6 months, then every 3 months for 2 years
• How to treat BKV nephropathy initially?

1. Reduce CNI first
2. Reduce antimetabolite first
3. Maintain CNI and convert antimetabolite to mTOR-i
4. Convert CNI to mTOR-I directly
5. Any of 1-4 and add adjunctive therapy (Cidifovir, Quinolone, Leflunomide and IVIG)
Reduction in maintenance immunosuppression is the best treatment for BKV nephropathy.

In patients with sustained high-level plasma BKV load despite adequately reduced immunosuppression, the adjunctive use of agents with antiviral activity (Cidofovir, Leflunomide, Sirolimus and/or Ciprofloxacin) may be considered.

Monitor serum creatinine in 1-2 week intervals, and BKV load in 2-4 week intervals.
When to restore baseline immunosuppression?

1. After clearance of viremia
2. After clearance of viremia and stabilized serum creatinine
3. After clearance of both viremia and SV40 positive cells from the tissue
4. After clearance of viremia, SV40 positive cells, and viruria
When to restore baseline immunosuppression?

There are difficulties to determine when to restore immunosuppression.

- Serum creatinine level does not decrease soon.
- On histological examinations, the inflammation score is unchanged in the first 3 months, it could include an immune reconstitution.
- Viruria sometimes sustain after clearance of BKV replication.

My recommendation is
- restore baseline immunosupression after clearance of viremia, stablized serum creatinine, clearance SV40 positive cells if you perform re-biopsy.
Conclusions

• As the mean age of transplant candidates rises, the number of recipients with pretransplant malignancies is expected to increase. Careful screening and follow up is important for long-term graft and patient survival.

• Screening for BKV replication in urine and blood are key recommendations for guiding us in reducing immunosuppression in patients with BKV viremia. More studies are needed to determine the efficacy of altering immunosuppressive medication regimens and of antiviral agents in the treatment of BKV nephropathy.