Kidney Transplant Outcomes of Patients With Multiple Myeloma

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Introduction: Data on kidney transplantation (KTx) outcomes of patients with multiple myeloma (MM) are very limited.

Methods: We investigated the outcomes of patients with MM who underwent KTx between 1994 and 2019.

Results: A total of 12 transplants from 11 patients were included. At the time of KTx, 6 were classified as having stringent complete response (CR), 2 as CR, 2 as very good partial response (VGPR), and 2 as partial response (PR). With a median follow-up of 40 (minimum–maximum, 5–92) months after KTx, hematologic progression occurred in 9 transplants (75%). There were 3 grafts (25%) that failed, and 5 patients (45.5%) experienced death with functioning allografts. Graft survival at 1 and 5 years was 82.5% and 66%, respectively. Progression-free survival (PFS) rates of the cohort at 1, 3, and 5 years were 83.3%, 55.6%, and 44.4%, respectively. The estimated median PFS of patients who received bortezomib at any time (pre-KTx and/or post-KTx) was not reached, whereas it was 24 months for those who never received bortezomib (P = 0.281). Overall survival (OS) rates of the cohort at 1, 3, and 5 years were 81.8%, 61.4%, and 61.4%, respectively. OS of patients who received bortezomib at any time was 87.5%, 72.9%, and 72.9%, and that for those who never received bortezomib was 66.7%, 33.3%, and 33.3% (P = 0.136). All deaths occurred owing to hematologic progression or treatment-related complications.

Conclusion: Kidney transplant outcomes of patients with myeloma who received bortezomib before or after KTx seem to be more favorable. Nevertheless, relapse after KTx in MM is still common. More studies are needed to better determine who benefits from a KTx.

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KEYWORDS: chronic kidney failure; graft survival; kidney transplantation; mortality; multiple myeloma; recurrence

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antibodies (daratumumab and elotuzumab), are now available. With the introduction of novel agents in the last 2 decades, the outcome of patients with MM has improved tremendously. A recent study found that the median survival has reached 7.7 years for patients under the age of 65 years since the utilization of newer drugs into the standard management of MM. According to a study using the US Renal Data System database by Reule et al., the incidence of renal replacement therapy from MM in the United States has decreased between 2001 and 2010, and clinically meaningful increases in survival have occurred for these patients.

Despite treatment with novel agents, a considerable number of patients with MM still develop end-stage kidney disease. Long-term dialysis for patients with myeloma has significant mortality risk and may prevent them from clinical trials for MM treatment, and significantly affecting their quality of life. Thus, we hypothesize that KTx in selected cases can improve the quality of life and may increase the OS of selected patients with MM without significant harm. In the subsequent texts, we report the outcomes of 12 kidney transplants in 11 patients with MM, review the previous literature, and compare them with our results.

**METHODS**

Patients with MM who underwent a KTx surgery between 1994 and 2019 at Mayo Clinic, Rochester, were included in this study. The study was exempted from the need for approval by the Mayo Clinic Institutional Review Board owing to the retrospective design, confidentiality of patient identity, and absence of invasive procedures, and informed consent was waived. The diagnosis of MM was based on the International Myeloma Working Group consensus criteria, and hematologic responses were evaluated according to the standard International Myeloma Working Group criteria (Supplementary Table S1). Serum and urine electrophoresis, serum and urine immunofixation studies, bone marrow examinations, and serum free light-chain measurements (κ, λ, and κ/λ ratio) were reviewed by hematologists before KTx, to evaluate hematologic response category. Frequencies of these tests were determined by the treating hematologist during post-transplant follow-up. Novel agents used in this study included the following: bortezomib, carfilzomib, ixazomib, lenalidomide, pomalidomide, and daratumumab. OS was measured from the date of KTx to death owing to any cause, or, if patients were alive, censored at the date of last visit. Progression free survival (PFS) was measured from the date of KTx to documented hematologic progression or death from any cause, whichever occurred first, or if alive without documentation of disease progression, censored for patients at the date of last disease evaluation. The protocol allograft biopsies, if available, were performed at implantation and 4-month, 1-year, 2-year, 5-year, and 10-year post-transplantation. Allograft histology result was evaluated according to the Banff criteria.20 Graft failure was defined as the loss of kidney allograft function leading to a permanent need for subsequent renal replacement therapy. Histologic examination of the protocol and clinical indication biopsies were based on light microscopic evaluation, immunofluorescence analysis, and electron microscopic examination.

**Statistical Analysis**

Continuous variables were expressed as median with the range of minimum and maximum. Discrete variables were expressed as proportions (number and percentage). Kaplan-Meier method and log-rank test were used to determine and compare estimated graft and patient survivals between patients who received bortezomib at any time (pre-KTx and/or post-KTx) versus those who was never treated with bortezomib. Because 1 patient underwent KTx twice, OS and PFS were evaluated per patient whereas graft survival was analyzed per grafts. A P < 0.05 was considered statistically significant. Cox regression analysis was performed to determine the effects of the time from the last hematologic response to KTx on OS, graft survival, and PFS. Statistical analysis was performed using STATA version 13.0 (Stata Corporation, College Station, TX).

**RESULTS**

**Demographic and Clinical Characteristics**

A total of 11 patients underwent 12 kidney transplants during the study period. The median age was 64 (range 53–70) years, and 7 (63.6%) were female. Monoclonal kappa light chain was present in 7 patients (63.6%). A total of 6 patients had a hemoglobin level of <10 g/dl, 5 had documented lytic bone lesions, and 1 had hypercalcemia at presentation with MM. Median plasma cell percentage in bone marrow biopsy was 30% (range 10–90). On native kidney histologic examination, 2 patients had cast nephropathy, 2 had cast nephropathy plus light-chain deposition disease, 3 had light-chain deposition disease, and 1 had light- and heavy-chain deposition disease. There were 3 patients who did not have a native kidney biopsy. One of the patients with light-chain deposition disease had 2 kidney transplants. Cytogenetic characteristics were available in 7 cases, all of which were compatible with standard-risk MM (Table 1). Transplant characteristics are found in Table 2.

The median time from the diagnosis of MM to KTx was 37 (9–195) months. There were 6 patients who
received novel agents and 8 who underwent hematopoietic stem-cell transplantation (SCT) before KTxs. The median time between SCT and KTxs was 32 (range 10–62) months. Hematologic response categories were stringent CR in 6, CR in 2, VGPR in 2, and the remaining 2 had PR before KTxs. Both of the patients with PR received only melphalan-based therapies before KTxs. The median time from last hematologic response to KTxs was 26 (6–60) months in the overall cohort, 26 (6–60) months in those who received bortezomib at any time (pre-KTxs and/or post-KTxs), and 26 (6–48) months in patients who never received bortezomib.

**Hematologic Progression and Histologic Relapses**

Follow-up data of patients are presented in Table 3. Clinical courses of each patient, treatment of relapse episodes, and outcomes after KTxs are found in Figure 1. Hematologic relapse occurred after KTxs in 9 cases (75%) during a median follow-up of 40 (5–92) months after KTxs. The estimated median relapse-free survival of all patients was 55 months from the last hematologic response and 26 months from the time of KTxs. The median time to hematologic relapse was 24 (range 1–79) months from the time of KTxs and 50 (20–87) months from the time of last hematologic response, which was achieved before KTxs. Regular protocol biopsies were available in 8 patients. Organ relapse (renal) was detected in 3 of 9 hematologic progression episodes (1, 6, and 35 months after KTxs), and graft loss occurred in 2 of these (2 and 6 months after KTxs). No association was found between time from the last hematologic response to KTxs and hematologic relapse (per month, odds ratio 0.98, 95% CI 0.94–1.03, \( P = 0.39 \)). The estimated median relapse-free survival in 8 transplants

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**Table 1. Baseline characteristics of patients with multiple myeloma who underwent a kidney transplant**

| Year of MM diagnosis | FLC | SPEP/IF | Bone marrow | FISH/cytogenetics | Hb | Bone lesion | Native kidney | Treatments before KTxs |
|----------------------|-----|--------|-------------|------------------|----|------------|--------------|------------------------|
| ID                   | Age | Sex | SP/E | Urine (%) | Serum | α | κ | λ | (κ/λ) | (%) |                   |
| 11a 53               | F   | 1993| n/a  | n/a       | n/a   | n/a| n/a| n/a| n/a | n/a | 10.7 Yes LCDD VAD |
| 6 64                 | F   | 1987| n/a  | n/a       | n/a   | n/a| n/a| n/a| n/a | 24  | 9.3 Yes LCDD Melphalan, prednisone |
| 9 70                 | F   | 1999| n/a  | n/a       | n/a   | n/a| n/a| n/a| n/a | 20  | 11.2 No Not done VBCMP |
| 11b 63               | F   | 1993| n/a  | n/a       | n/a   | n/a| n/a| n/a| n/a | n/a |                   |
| 10 64                | F   | 1991| 1.55 | 2.11      | 0.73  | n/a| n/a| n/a| n/a | 9.5 Yes Cast nephropathy plus LCDD Melphalan/prednisone, thalidomide/dexamethasone, PLEX VBCMP |
| 8 68 M               | 2007| 432 | 8.94 | 48.3     | n/a   | n/a| n/a| n/a| n/a | 70  | 11.3 Yes LCDD Bortezomib, lenalidomide, ASCT |
| 7 62 F               | 2009| 2.33| 2550 | 0.0009   | n/a   | n/a| n/a| n/a| n/a | 90  | 9.7 No Cast nephropathy Bortezomib, ASCT |
| 1 58 M               | 2014| 23.6| 2.73 | 8.64     | n/a   | n/a| n/a| n/a| n/a | 10  | 8.8 No LHDD CyBoRd, lenalidomide, dexamethasone |
| 5 70 F               | 2014| 14  | 1400 | 0.01     | n/a   | n/a| n/a| n/a| n/a | 30  | 9.6 No Not done Bortezomib, dexamethasone, ASCT |
| 2 59 F               | 2005| 12.3| 16.5 | 0.7455   | n/a   | n/a| n/a| n/a| n/a | 60  | 10.4 No Not done Bortezomib, dexamethasone, ASCT |
| 3 69 M               | 2015| 103.25| 24.7 | 4.17     | n/a   | n/a| n/a| n/a| n/a | 30  | 7.4 Yes Cast nephropathy Bortezomib, dexamethasone, thalidomide, ASCT |
| 4 64 M               | 2015| 0.936| 1040 | 0.0009   | n/a   | n/a| n/a| n/a| n/a | 60  | 11.5 No Cast nephropathy plus LCDD VRD, ASCT |

ASCT, autologous stem-cell transplantation; CyBoRd, cyclophosphamide, bortezomib, dexamethasone; F, female; FISH, fluorescence in situ hybridization; FLC, free light chain; Hb, hemoglobin; ID, identification; IF, immunofixation; KTxs, kidney transplantation; LCDD, light-chain deposition disease; LHCDD, light- and heavy-chain deposition disease; M, male; MM, multiple myeloma; n/a, not available (owing to the unavailability of some studies in old era); PLEX, plasma exchange; SPEP, serum protein electrophoresis; VAD, vincristine, adriamycin, dexamethasone; VBCMP, vincristine, carmustine, melphalan, cyclophosphamide, and prednisone; VRD, bortezomib, lenalidomide, and dexamethasone.

*First kidney transplantation of the same patient. Age is at the time of kidney transplantation.

*Second kidney transplantation of the same patient. Age is at the time of kidney transplantation.

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**Table 2. Kidney transplant data of patients**

| Transplant characteristics | N (%) |
|----------------------------|-------|
| Age, median, range (min–max) | 64 (53–70) |
| Female sex, n (%) | 7 (64) |
| Donor, n (%) | 3 (25) |
| Living-related | 9 (75) |
| Deceased | 3 (25) |
| Induction immunosuppression, n (%) | 8 (67) |
| Basiliximab | 4 (33) |
| Antithymocyte globulin | 4 (33) |
| Maintenance immunosuppression, n (%) | 8 (67) |
| Tacrolimus-MMF-prednisone | 2 (17) |
| Cyclosporine-MMF-prednisone | 1 (8) |
| Rapamycin-MMF-prednisone | 1 (8) |
| Belatacept-MMF-prednisone | 1 (8) |

MMF, mycophenolate mofetil.
Table 3. Follow-up characteristics of patients with multiple myeloma after the kidney transplantation

| ID       | KTx year | Donor type | Months from the last hematologic response to KTx | Maintenance after KTx | Biochemical relapse | Histologic relapse | Organ (renal) relapse | Relapse treatments | Hematologic response | Renal response | Follow-up (mo) | Graft loss | Mortality |
|----------|----------|------------|-------------------------------------------------|-----------------------|---------------------|---------------------|---------------------|--------------------|---------------------|----------------|---------------|------------|-----------|
| 1        | 1994     | Living     | 6                                               | PR                    | No                  | Yes (24 mo)         | No                  | No                 | VBCMP               | PR              | No organ relapse | 48         | No        |
| 2        | 1997     | Deceased   | 48                                               | CR/VGPR               | No                  | Yes (2 mo)          | No                  | No                 | Melphalan           | Stable disease   | No organ relapse | 5          | No        |
| 3        | 2007     | Living     | 34                                               | sCR (negative IHC)    | No                  | Yes (35 mo)         | Yes                 | Yes                | None                | Stable disease   | Stable disease  | 80         | No        |
| 4        | 2018     | Deceased   | 60                                               | sCR (MRD—0.15%)       | No                  | No                  | No                 | No                 | Lenalidomide        | No              | No organ relapse | 61         | No        |
| 5        | 2017     | Living     | 29                                               | sCR (negative IHC)    | No                  | Yes (27 mo)         | No                  | No                 | Observation         | Stable disease   | No organ relapse | 44         | No        |
| 6        | 2010     | Living     | 14                                               | CR/VGPR               | No                  | Yes (6 mo)          | No                  | Yes                | Bortezomib based   | Progressive disease | 8           | At 6 mo (plasma cell infiltration) | Yes (hematologic progression) |
| 7        | 2015     | Died       | 58                                               | sCR (MASS-FIX negative) | No                  | No                  | No                 | No                 | No                  | No organ relapse | 72         | No         |
| 8        | 2016     | Living     | 6                                                | Lenalidomide          | No                  | No                  | No                 | No                 | No                  | No organ relapse | 61         | No         |
| 9        | 2002     | Living     | 18                                               | PR                    | No                  | Yes (29 mo)         | No                  | No                 | Dexamethasone       | Stable disease   | No organ relapse | 35         | No        |
| 10       | 2017     | Living     | 29                                               | sCR (negative IHC)    | No                  | Yes (12 mo)         | Yes                | No                 | Observation         | Stable disease   | No organ relapse | 36         | No        |
| 11       | 2015     | Living     | 23                                               | sCR (Mass-FIX negative) | No                  | No                  | No                 | No                 | No                  | No organ relapse | 20         | No         |
| 12       | 2016     | Living     | 28                                               | Lenalidomide          | Yes (1 mo)          | No                  | Yes                | Daratumumab         | Responded but eventually relapsed | Graft loss     | 17          | At 2 mo (primary nont, bleeding) | No         |

CR, complete response; ID, identification; IHC, immunohistochemistry (by bone marrow biopsy); KTx, kidney transplantation; MDS, myelodysplastic syndrome; MRD, minimal residual disease; n/a, not available; PR, partial response; sCR, stringent complete response; VBCMP, vincristine, carbustine, melphalan, cyclophosphamide, and prednisone; VGPR, very good partial response.
with a waiting time to KTx of \( \leq 1 \) year versus 4 transplants with a waiting time of \( > 1 \) year was comparable (24 months versus 26 months, \( P = 0.748 \)). The estimated median relapse-free survival of 3 patients treated with maintenance for MM was 12 months versus 29 months for 9 transplants who did not receive maintenance for MM (\( P = 0.732 \)). Median relapse-free survival from the time of KTx was 26 months in patients who received novel agents before KTx and 29 months for those who did not receive novel agents before KTx (\( P = 0.936 \)). It was 72 and 50 months from the time of last hematologic response (before KTx) for the same groups, respectively (\( P = 0.460 \)). It was 24 and 35 months for patients who did not receive a SCT versus those who underwent a SCT, respectively (\( P = 0.204 \)).

Among the 9 kidney transplants with hematologic relapse episodes, 1 patient received melphalan-based therapy 2 months after KTx. Unfortunately, the patient developed hematologic progression and died 5 months after KTx. One achieved a PR after VBCMP (vincristine, carmustine, melphalan, cyclophosphamide, and prednisone) chemotherapy. One patient was treated with dexamethasone but eventually progressed. Bortezomib-based treatment was used in 2 patients; 1 did not respond and developed progression, whereas the other 1 achieved VGPR. Another patient is currently being treated with daratumumab as maintenance therapy. There were 3 patients who did not receive chemotherapy for hematologic progression episodes after KTx, of whom 2 had a biochemical relapse and hematologic parameters (by free light-chain levels and immunofixation studies) remained stable during the follow-up of 17 and 24 months after relapse, respectively. In the other patient who did not receive clone-directed therapy for relapse, monotypic kappa light-chain deposits were defined in tubular basement membranes without decline in renal function consistent with early recurrence of light-chain deposition disease.21 Although an M-spike in serum protein electrophoresis re-emerged, this was regarded as clinically insignificant, and this patient died from infectious
complications 44 months after the relapse, with a functioning allograft.

In most patients who required clone-directed therapy for relapsing myeloma after the KTx, mycophenolate mofetil was discontinued and the dose of glucocorticoids (which were usually part of the management of clone-directed therapies) was increased.

**Graft Failure**

Median death-censored graft survival was not reached in the overall cohort. Graft survival at 1, 3, and 5 years was 82.5%, 82.5%, and 66%, respectively. Graft failure occurred in 3 transplants (25%). The first one was from a living donor, and the patient achieved CR after autologous SCT before KTx. Primary allograft non-function occurred, multiple red blood cell transfusions were given owing to recurrent hemorrhage, and eventually graft nephrectomy was performed 2 months after KTx because of renal vein thrombosis. In this case, there were also signs of biochemical relapse. The second allograft was also from a living donor, and the patient had achieved CR before KTx after undergoing autologous SCT. After a diagnosis of Banff IB acute cellular rejection on 4-month protocol biopsy, hematologic progression occurred and the graft failed 6 months after KTx owing to plasma cell infiltration of the kidney. The third graft failed 48 months after KTx owing to chronic allograft nephropathy. Patient’s hematologic response before KTx was PR, and she received chemotherapy for relapse 2 years after KTx. Banff IIA acute cellular rejection followed the recovery of hematopoietic cells, after the treatment of myeloma.

Death-censored graft survival among patients who received maintenance therapy for MM versus no maintenance was comparable. Median graft survival was not reached for either group. The 3-year graft survival rates were 66.7% versus 87.5%, whereas 5-year survival rates were 66.7% versus 65.6%, respectively ($P = 0.623$). Death-censored graft survival at 3 years in patients who received novel agents before KTx versus those who did not was 71.4% versus 66.7%, respectively ($P = 0.624$), and these rates were the same at 5 years. Death-censored graft survival of patients who received a SCT before KTx versus those who did not undergo SCT was 77.8% versus 100% at 3 years ($P = 0.623$). Time from the last hematologic response to KTx did not have a significant impact on the risk of graft loss (per month, odds ratio 0.96, 95% CI 0.86–1.07, $P = 0.43$).

**Patient Survival**

The estimated median PFS of the cohort was 44 (CI 18–70) months. PFS of the cohort at 1, 3, and 5 years was 83.3%, 55.6%, and 44.4%, respectively. PFS rates at 1, 3, and 5 years for those who received bortezomib at any time (pre-KTx and/or post-KTx) were 87.5%, 72.9%, and 54.7%, respectively, whereas PFS rates for those who never received bortezomib were 75%, 50%, and 25%, respectively ($P = 0.281$; Figure 2). The median estimated PFS was not reached in the former group, whereas it was 24 months in the latter group.

In the median follow-up of 40 (5–92) months, death occurred in 6 patients (54.5%). OS rates of the cohort at 1, 3, and 5 years were 81.8%, 61.4%, and 61.4%, respectively.
respectively. The estimated median OS of patients who received bortezomib at any time was 92 months, whereas it was 35 months for those who was never treated with bortezomib ($P = 0.136$; Figure 3). The 1-, 3-, and 5-year OS rate of the former group was 87.5%, 72.9%, and 72.9%, whereas it was 66.7%, 33.3%, and 33.3% at the same time periods for the latter group, respectively.

Patients who achieved a stringent CR before KTx had a longer OS (median 80 versus 35 months), but this was not significant ($P = 0.445$). OS rates among patients who received maintenance versus those who did not were comparable ($P = 0.215$). The median OS was not reached in patients who received novel agents before KTx, whereas it was 35 months in those who were not treated with novel agents ($P = 0.579$). The estimated median OS of 2 patients who did not receive SCT (excluding the first allograft of the patient who underwent kidney transplant twice, because OS is measured per patient and not per kidney transplant) was 5 months versus 80 months for those who underwent a SCT before KTx ($P = 0.034$). Causes of death were sepsis ($n = 2$), hematologic progression ($n = 2$), sepsis plus myelodysplastic syndrome ($n = 1$), and therapy-related myeloid neoplasia ($n = 1$). The patient who underwent KTx twice had achieved a VGPR before the second KTx. She developed myelodysplastic syndrome, underwent a stem-cell transplant, and died owing to septic complications 92 months after the second KTx. Of 9 patients who experienced hematologic progression after KTx, 5 died at a median of 5 (range 1–48) months after relapse. The remaining 4 patients with hematologic progression were alive at the end of a median of 21 (range 16–24) months of follow-up after relapse. Time from the last hematologic response to KTx did not affect OS significantly (per month, odds ratio 0.98, 95% CI 0.93–1.03, $P = 0.457$).

Other complications after KTx are summarized in Table 4.

### DISCUSSION

Despite the increasing efficacy of current therapies, patients with MM still develop end-stage kidney disease. Renal replacement therapy with dialysis affects dosing of some medications and is an exclusion in clinical trials, including chimeric antigen receptor T-cell therapy, which can negatively affect survival. Kidney transplantation, if feasible, is the most beneficial form of renal replacement therapy for these patients; however, graft loss and early mortality owing to MM are major challenges to KTx in these patients. Therefore, data on KTx in patients with MM are limited and mostly come from single case reports and small series. The largest of these reported on 13 patients across all of France, who underwent KTx but only 10 of them had MM at the time of KTx. This series is the largest single-center study on the outcomes of patients with symptomatic MM after kidney transplant.

In this study, the 3-year OS after kidney transplant was 61.4%, even though nearly all patients had relapse. Antimyeloma therapy was generally well tolerated without significant side effects despite coadministration with immunosuppression. Even in this small case series, there was a longer OS in patients who...
Table 4. Other complications after kidney transplantation

| Complication                                      | Management/comment                                                                 | Outcome          |
|--------------------------------------------------|-------------------------------------------------------------------------------------|------------------|
| Hematologic                                      | -Therapy-related, FLT-3 negative with monosomy 7 and a ring chromosome 7            | -Death           |
| -Acute myeloid leukemia (patient 3)              | -Allogeneic SCT                                                                     | -No response and death |
| -Myelodysplastic syndrome (patient 11, second KTx) | -Owing to lenalidomide maintenance, drug discontinued                              | -Improved        |
| -Transfusion-dependent anemia and thrombocytopenia (patient 2) | -Presumed to occur secondary to lenalidomide maintenance, drug discontinued     | -Improved        |
| -Anemia and neutropenia (patient 1)              |                                                                                     |                  |
| Rejection                                        | -Attributed to recovery of immune system which was suppressed by chemotherapy, following a hematologic relapse (Banff IIIB) | -Graft loss 2 yr after the rejection |
| -Patient 11 (first KTx)                          | -Presumed to occur from frequent change in maintenance immunosuppression (MMF discontinuation and switch from tacrolimus to rapamycin due to skin cancer and BK viremia, lenalidomide maintenance may have also contributed) | -Kidney functions remained stable for >5 yr after the rejection |
| -Patient 1 (multiple acute rejection episodes between 6 and 12 mo after the kidney transplantation) |                                                                                     |                  |
| Infection                                        | -MMF discontinuation                                                                  | -Improvement      |
| -BK viremia, no nephropathy (patient 1)          | -MMF discontinued, cidofovir                                                          | -Improvement      |
| -BK nephropathy, EBV viremia (patient 7)         | -Intensive care                                                                      | -Death           |
| -Pneumonia → sepsis (patient 10)                 | -Intensive care                                                                      | -Death           |
| -Pneumonia → sepsis (patient 9)                  |                                                                                     |                  |
| Malignancy (other than hematologic)              | -MMF discontinued (concurrent BK viremia), tacrolimus was switched to rapamycin     | -SCC recurred    |
| -Squamous cell (SCC) skin cancer (patient 1)     |                                                                                     |                  |
| Other                                            | -Anticoagulation                                                                     | -Graft nephrectomy |
| -Allograft vein thrombosis with bilateral deep vein thrombosis in lower extremities (patient 4) | -Owing to myeloma                                                                   |                  |
| -Persistent hypercalcemia (patient 6)            | -Prednisone discontinued                                                             |                  |
| -Aseptic necrosis of the femoral head (patient 11, second KTx) | -Observation, no surgery needed                                                      |                  |
| -Urinary leak (patient 11, second KTx)           | -Observation                                                                         |                  |
| -Lymphocele (patient 10)                         |                                                                                     |                  |

EBV, Epstein-Barr virus; KTx, kidney transplantation; MMF, mycophenolate mofetil; SCT, stem-cell transplantation.

achieved ≥VGPR before KTx compared with PR. The depth of hematologic response, however, did not affect graft survival. Because MM is not curable currently, it was not surprising that no difference was found between the wait time after achieving a hematologic response and outcomes. Unlike solid cancers and even particular types of lymphomas, the risk of relapse in patients with MM does not decrease over time.41 We could not find a significant association between time from last hematologic response to KTx with major patient outcomes. This was not significant when we compared groups with a waiting time of ≤1 year versus >1 year; however, our sample size was small to have statistical power.

Because of the incurable nature of MM, even patients who achieved a CR eventually had a relapse.41 The effect of maintenance therapy on PFS could not be demonstrated owing to the small number of patients using maintenance. Acute cellular rejection had been a concern with immunomodulatory drugs as cases of treatment-resistant rejection have been reported.33 One patient in our cohort developed acute rejection during the maintenance therapy with lenalidomide, but mycophenolate mofetil was discontinued before rejection owing to BK polyomavirus nephropathy. This may have contributed to the rejection. No other patient on either maintenance or treatment with immunomodulatory drugs had a rejection. We were unable to evaluate whether minimal residual disease or MASS-FIX (monoclonal protein detection by mass spectrometry) could predict a longer time to relapse as these tests were mostly unavailable to this cohort. Nevertheless, future studies should evaluate these techniques in this population.

It is important to note that not all relapse episodes were treated successfully, and relapsing disease was the leading contributor to death in a considerable number of patients. Patients who received bortezomib seemed to have a longer PFS and OS, although these were not statistically significant and likely a reflection of the small sample size. A strategy of combined allogeneic SCT and KTx from the same donor has been investigated. The approach has been found to provide graft versus myeloma effect which may increase PFS at the same time offer the advantage of not requiring post-KTx immunosuppression owing to utilization of both grafts from the same donor.42–44 Logistically though, this approach is not widely available given the requirement for an HLA-matched donor for both organs. Fortunately, as more therapies become available for MM most recently with the approval of the Food and Drug Administration of chimeric antigen receptor T-cell therapy, we should see continued improvement in the OS.

Despite its risks, KTx will be an important option of renal replacement therapy for patients with MM owing to the inferior OS of patients with MM on dialysis. The most important aspect is selecting the patients who would benefit the most and would have
the lowest risk of disease relapse. Some suggest incorporating cytogenetic characteristics and minimal residual disease into pretransplant selection criteria for patients with MM.\textsuperscript{47} Cytogenetics by fluorescence in situ hybridization on the bone marrow at diagnosis discriminates high-risk patients from standard-risk patients with myeloma, which is associated with survival.\textsuperscript{46} Cytogenetic characteristics were available in a subset of our patients, but all were compatible with survival.\textsuperscript{46} Unfortunately, we did not have the minimal residual disease status on our cohort at the time of kidney transplant.

Our case series does not have the power to reach a solid conclusion, but even in this small series, there is a trend toward significance among those who received kidney allograft more recently as compared with the old era. We think that this may be related to the introduction of novel agent and the increased probability of reaching a stringent CR before kidney transplant. Although this is a small single-center study, this is the largest study of patients with symptomatic myeloma with kidney transplant to date. One of the major findings of our study is that patients with myeloma who received bortezomib at any time did better than those who were never treated with bortezomib. Another is the lack of benefit of longer waiting time, unlike in solid cancers. Both these findings will need to be confirmed. Additional studies will also be needed to provide answers to the best maintenance therapy for patients with kidney transplant. Studies will also be needed to determine the minimum response required for patients to undergo KTxs. These answers will hopefully provide a clear algorithm for selecting the patients for KTxs. Although KTxs cannot be recommended for all patients with MM who develop end-stage renal disease, our study suggests that long-term allograft and patient survival can be achieved and will likely improve as more effective therapies for myeloma develop.

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**AUTHOR CONTRIBUTIONS**

CH, AB, MPA, and NL created the concept and design of the study. CH collected data and provided statistical analysis. CH, AB, MPA, HA, FKB, AD, DD, MAG, NI, PK, AK, SK, EL, SVR, CS, and NL interpreted the results. CH wrote the manuscript. AB, MPA, HA, FKB, AD, DD, MAG, NI, PK, AK, SK, EL, SVR, CS, and NL revised the manuscript for important intellectual content. AB, MPA, HA, FKB, AD, DD, MAG, NI, PK, AK, SK, EL, SVR, CS, and NL approved the final version. NL supervised.

**SUPPLEMENTARY MATERIAL**

**Table S1.** Standard IMWG (International Myeloma Working Group) response criteria.

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