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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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Kidney involvement is frequently found in multiple myeloma (MM). In fact, MM is the most common type of nonurologic malignancy to cause renal impairment.[1] Using serum creatinine and cystatin C as measurements of renal function, the frequency of newly diagnosed patients presenting with an estimated glomerular filtration rate of <30 ml/min per 1.73 m^2 was 17% in 1 study.[2] Patients with MM and acute kidney injury are reported to have worse survival compared with patients with MM and normal renal function.[3] Despite modern therapies, patients with myeloma with end-stage kidney disease continue to have inferior survival.[4] Moreover, although improvement in kidney function with antimyeloma therapy is associated with improved survival, it is still inferior to patients who have normal kidney function at baseline.[5] In the general population, KTx is the best option for renal replacement therapy in terms of quality of life measures and overall survival (OS) in carefully selected subjects.[6,7] KTx is rarely performed in MM owing to the risk of relapse, graft loss, rejection, and concerns of immunosuppression hastening relapse and early mortality. Only case reports or small case series are available so far.[8–12] Numerous options of novel agents for MM, including immunomodulatory drugs (lenalidomide and pomalidomide), proteasome inhibitors (bortezomib, carfilzomib, ixazomib), histone deacetylase inhibitor (panobinostat), and monoclonal

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antibodies (daratumumab and elotozumab), are now available.[13] With the introduction of novel agents in the last 2 decades, the outcome of patients with MM has improved tremendously.[14,15] 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.[16] According to a study using the US Renal Data System database by Reule *et al.*,[17] 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,[18] and hematologic responses were evaluated according to the standard International Myeloma Working Group criteria (Supplementary Table S1).[19] 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

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

ID	Age /sex	Year of MM diagnosis	FLC			SPEP/IF		Bone marrow (%)	FISH/cytogenetics	Hb	Bone lesion	Native kidney	Treatments before KTx
			κ	λ	κ/λ	Serum	Urine						
11[a]	53 F	1993	n/a	n/a	n/a	IgGλ	Not done	n/a	n/a	10.7	Yes	LCDD	VAD
6	64 F	1987	n/a	n/a	n/a	κ	Negative	24	n/a	9.3	Yes	LCDD	Melphalan, prednisone
9	70 F	1999	n/a	n/a	n/a	IgGλ	Not done	20	n/a	11.2	No	Not done	VBCMP
11[b]	63 F	1993	n/a	n/a	n/a	—	—	—	—	—	—	—	VBCMP
10	64 F	1991	1.55	2.11	0.73	IgGκ	Not done	20	n/a	9.5	Yes	Cast nephropathy plus LCDD	Melphalan/prednisone thalidomide/dexamethasone, PLEX
8	68 M	2007	432	8.94	48.3	κ	Not done	70	Inv q2 and t(11;14)	11.3	Yes	LCDD	Bortezomib, lenalidomide, ASCT
7	62 F	2009	2.33	2550	0.0009	λ	λ	90	Loss of q14 and p4 and copy 13	9.7	No	Cast nephropathy	Bortezomib, ASCT
1	58 M	2014	23.6	2.73	8.64	IgGκ	IgGκ	10	Trisomy 9 and 15	8.8	No	LHCDD	CyBorD, lenalidomide, dexamethasone
5	70 F	2014	14	1400	0.01	IgAλ	IgAλ	30	Normal	9.6	No	Not done	Bortezomib, dexamethasone, ASCT
2	59 F	2005	12.3	16.5	0.7455	IgAκ	IgAκ	60	Trisomy 9 and 11	10.4	No	Not done	Bortezomib, dexamethasone, ASCT
3	69 M	2015	103.25	24.7	4.17	IgGκ	IgGκ	30	t (11;14)	7.4	Yes	Cast nephropathy	Bortezomib, dexamethasone, thalidomide, ASCT
4	64 M	2015	0.936	1040	0.0009	IgAλ	IgAλ	60	t (11;14)	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; KTx, 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.
[a]First kidney transplantation of the same patient. Age is at the time of kidney transplantation.
[b]Second kidney transplantation of the same patient. Age is at the time of kidney transplantation.

received novel agents and 8 who underwent hematopoietic stem-cell transplantation (SCT) before KTx. The median time between SCT and KTx 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 KTx. Both of the patients with PR received only melphalan-based therapies before KTx. The median time from last hematologic response to KTx was 26 (6–60) months in the overall cohort, 26 (6–60) months in those who received bortezomib at any time (pre-KTx and/or post-KTx), and 26 (6–48) months in patients who never received bortezomib.

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* (%)	
Living-related	9 (75)
Deceased	3 (25)
Induction immunosuppression, *n* (%)	
Basiliximab	8 (67)
Antithymocyte globulin	4 (33)
Maintenance immunosuppression, *n* (%)	
Tacrolimus-MMF-prednisone	8 (67)
Cyclosporine-MMF-prednisone	2 (17)
Rapamycin-MMF-prednisone	1 (8)
Belatacept-MMF-prednisone	1 (8)

MMF, mycophenolate mofetil.

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 KTx are found in Figure 1. Hematologic relapse occurred after KTx in 9 cases (75%) during a median follow-up of 40 (5–92) months after KTx. The estimated median relapse-free survival of all patients was 55 months from the last hematologic response and 26 months from the time of KTx. The median time to hematologic relapse was 24 (range 1–79) months from the time of KTx and 50 (20–87) months from the time of last hematologic response, which was achieved before KTx. 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 KTx), and graft loss occurred in 2 of these (2 and 6 months after KTx). No association was found between time from the last hematologic response to KTx 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

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	Hematologic response during KTx	Maintenance after KTx	Biochemical relapse	Histologic relapse	Organ (renal) relapse	Relapse treatments	Hematologic response	Renal response	Follow-up (mo)	Graft loss	Mortality
11—first KTx)	1994	Living	6	PR	No	Yes (24 mo)	No	No	VBCMP	PR	No organ relapse	48	48 mo (chronic allograft nephropathy)	No
6	1997	Deceased	48	CR/VGPR	No	Yes (2 mo)	No	No	Melphalan	Progressive disease	No organ relapse	5	No	Yes (hematologic progression)
9	2002	Living	18	PR	No	Yes (29 mo)	No	No	Dexamethasone	Stable disease	No organ relapse	35	No	Yes (sepsis)
10	2007	Living	34	sCR (negative IHC)	No	Yes (35 mo)	Yes	Yes	None	Stable disease	Stable disease	80	No	Yes (pneumonia, sepsis)
11—second KTx	2004	Living	8	VGPR	No	Yes (79 mo)	No	No	Melphalan + prednisone, bortezomib, lenalidomide	VGPR	No organ relapse	92	No	Yes (MDS, sepsis)
8	2010	Living	14	CR/VGPR	No	Yes (6 mo)	No	Yes	Bortezomib based	Progressive disease	Progression	8	At 6 mo (plasma cell infiltration)	Yes (hematologic progression)
7	2015	Deceased	58	sCR (MASS-FIX negative)	No	No	No	No	No relapse	No relapse	No organ relapse	72	No	No
1	2016	Living	6	VGPR (MRD—0.15%)	Lenalidomide	No	No	No	No relapse	No relapse	No organ relapse	61	No	No
5	2017	Living	29	sCR (negative IHC)	No	Yes (27 mo)	No	No	Observation	Stable	No organ relapse	44	No	No
2	2018	Deceased	60	sCR (MRD—0.0016%)	Lenalidomide	Yes (12 mo)	No	No	Observation	Stable	No organ relapse	36	No	No
3	2018	Living	28	sCR (MASS-FIX negative)	No	No	No	No	No relapse	No relapse	No organ relapse	20	No	Yes (myeloid neoplasm)
4	2019	Living	23	sCR (MRD—0.0045%)	Lenalidomide	Yes (1 mo)	No	Yes	Daratumumab	Responded but eventually relapsed	Graft loss	17	At 2 mo (primary nonf, 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, carmustine, melphalan, cyclophosphamide, and prednisone; VGPR, very good partial response.

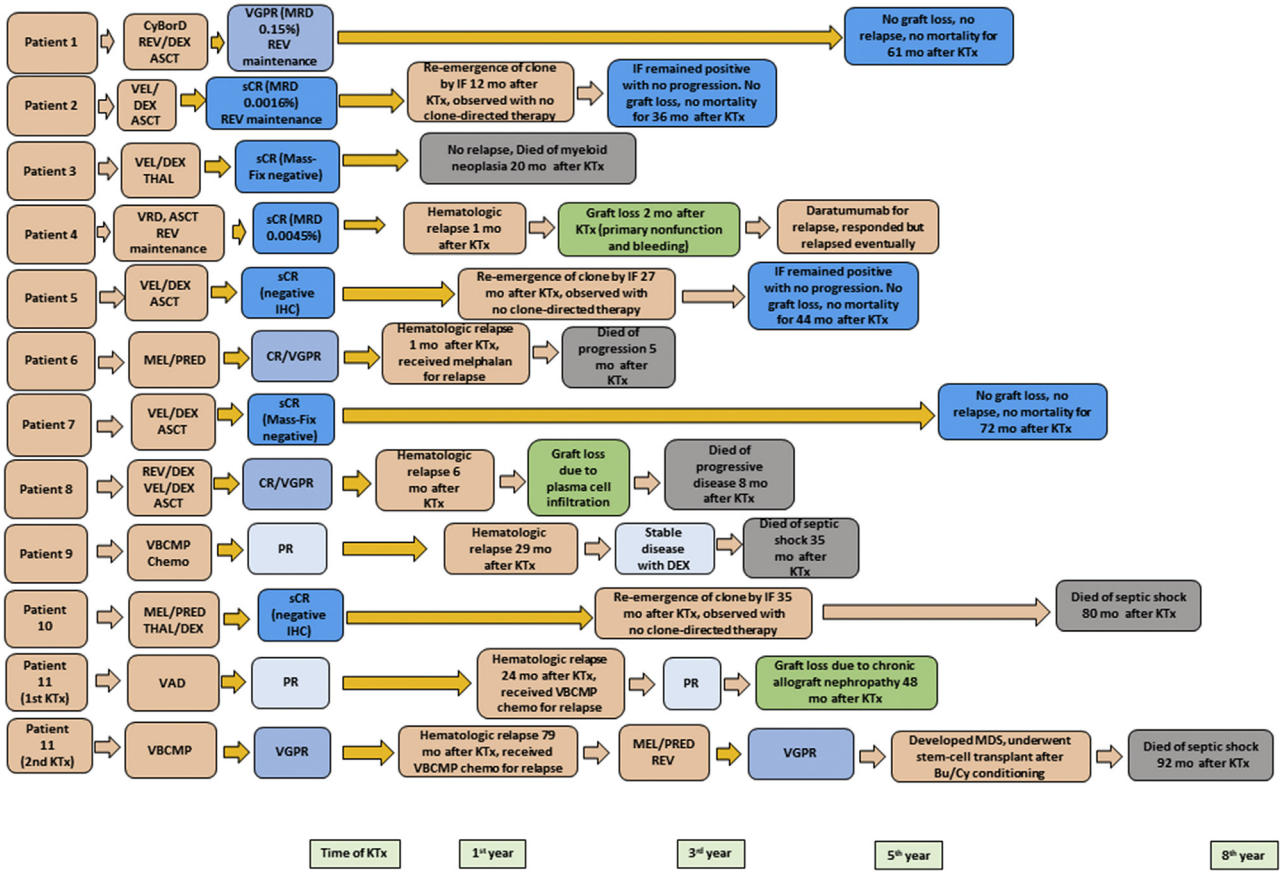

Figure 1. Courses of each patient after kidney transplantation. Timing of relapse episodes, their treatments, and outcomes for kidney allografts and patients are also revealed. Protocol biopsies were available except patients 1, 2, and 11 (both first and second transplants). ASCT, autologous stem-cell transplantation; CR, complete response; CyBorD, cyclophosphamide/bortezomib/dexamethasone; DEX, dexamethasone; KTx, kidney transplantation; IF, immunofixation; IHC, immunohistochemistry (of bone marrow); MDS, myelodysplastic syndrome; MRD, minimal residual disease; PR, partial response; PRED, prednisone; REV, lenalidomide; sCR, stringent complete response; THAL, thalidomide; VAD, vincristine, adriamycin, dexamethasone; VBCMP, vincristine, carmustine, melphalan, cyclophosphamide, and prednisone; VEL, bortezomib; VGPR, very good partial response; VRD, bortezomib/lenalidomide/dexamethasone.

with a waiting time to KTx of ≤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

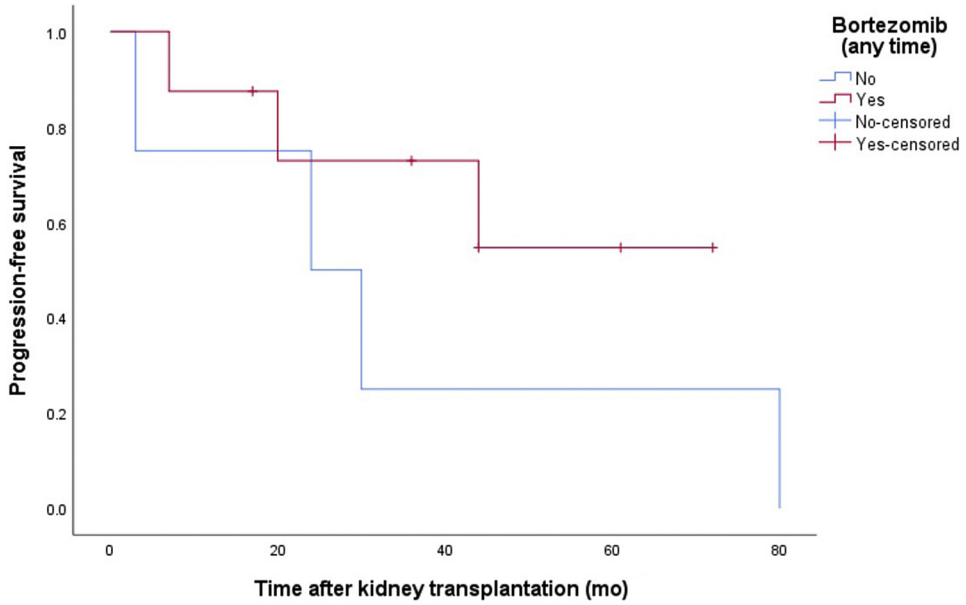

Figure 2. PFS rates at 1, 3, and 5 years of patients who received bortezomib at any time were 87.5%, 72.9%, and 54.7%, whereas PFS rates of patients who never received bortezomib were 75%, 50%, and 25%, respectively ($P = 0.281$). PFS, progression-free survival.

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 nonfunction 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%,

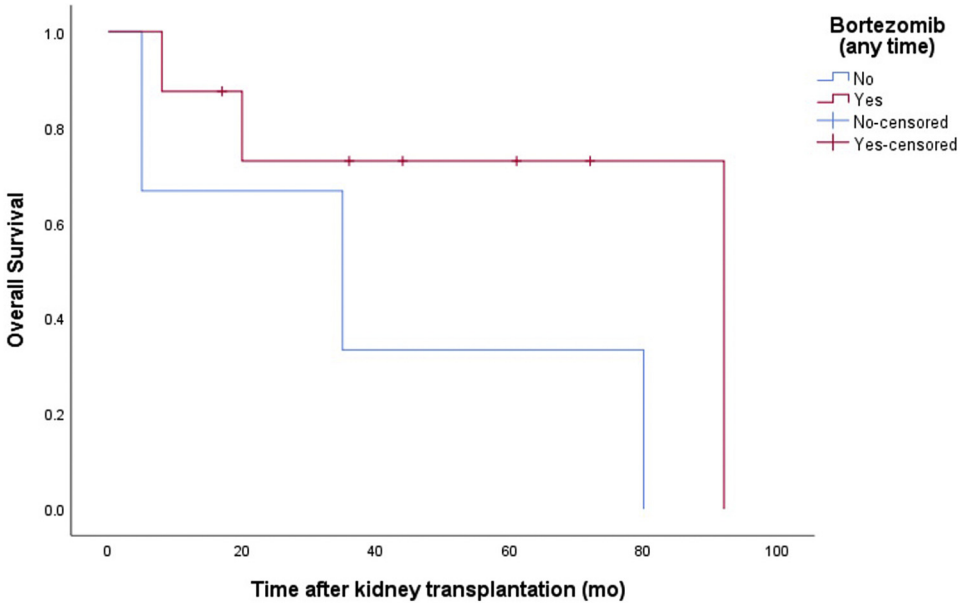

Figure 3. The 1-, 3-, and 5-year OS rates of patients who were treated with bortezomib at any time were 87.5%, 72.9%, and 72.9%, whereas OS rates for those who never received bortezomib were 66.7%, 33.3%, and 33.3%, respectively ($P = 0.136$). OS, overall survival.

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.[22–24] 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.[12] Therefore, data on KTx in patients with MM are limited and mostly come from single case reports and small series.[7–12,25–40] The largest of these reported on 13 patients across all of France,[12] 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 -Acute myeloid leukemia (patient 3) -Myelodysplastic syndrome (patient 11, second KTx) -Transfusion-dependent anemia and thrombocytopenia (patient 2) -Anemia and neutropenia (patient 1)	-Therapy-related, FLT-3 negative with monosomy 7 and a ring chromosome 7 -Allogeneic SCT -Owing to lenalidomide maintenance, drug discontinued -Presumed to occur secondary to lenalidomide maintenance, drug discontinued	-Death -No response and death -Improved -Improved
Rejection -Patient 11 (first KTx) -Patient 1 (multiple acute rejection episodes between 6 and 12 mo after the kidney transplantation)	-Attributed to recovery of immune system which was suppressed by chemotherapy, following a hematologic relapse (Banff IIB) -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)	-Graft loss 2 yr after the rejection -Kidney functions remained stable for >5 yr after the rejection.
Infection -BK viremia, no nephropathy (patient 1) -BK nephropathy, EBV viremia (patient 7) -Pneumonia > sepsis (patient 10) -Pneumonia > sepsis (patient 9)	-MMF discontinuation -MMF discontinued, cidofovir -Intensive care -Intensive care	-Improvement -Improvement -Death -Death
Malignancy (other than hematologic) -Squamous cell (SCC) skin cancer (patient 1)	-MMF discontinued (concurrent BK viremia), tacrolimus was switched to rapamycin	-SCC recurred
Other -Allograft vein thrombosis with bilateral deep vein thrombosis in low extremities (patient 4) -Persistent hypercalcemia (patient 6) -Aseptic necrosis of the femoral head (patient 11, second KTx) -Urinary leak (patient 11, second KTx) -Lymphocele (patient 10)	-Anticoagulation -Owing to myeloma -Prednisone discontinued -Observation, no surgery needed -Observation	-Graft nephrectomy -Expired owing to hematologic progression

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.[45] 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.[46] Cytogenetic characteristics were available in a subset of our patients, but all were compatible with standard-risk MM. Minimal residual disease testing after treatment may also help identify patients with the longest PFS.[47] 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 KTx. These answers will hopefully provide a clear algorithm for selecting the patients for KTx. Although KTx 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.

DISCLOSURE

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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

Supplementary File (PDF).

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

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