



ORIGINAL ARTICLE

Risk of relapse of multiple myeloma following kidney transplantation

Sapna Shah¹, Maria Ibrahim², Michael Delaney³, Steve Schey², Ceri Bygrave⁴, Matthew Streetly⁵ and Reuben Benjamin²

¹King's College London, London, UK, ²King's College Hospital NHS Trust, London, UK, ³East Kent Hospital University NHS Foundation Trust, Kent, UK, ⁴Cardiff and Vale University Health Board, Cardiff, UK and ⁵Guy's and St Thomas' NHS Foundation Trust, London, UK

Correspondence and offprint requests to: Sapna Shah; E-mail: sapna.shah@nhs.net

ABSTRACT

Background. Autologous stem cell transplantation (ASCT) and novel therapies have improved the prognosis for patients with multiple myeloma (MM). For those who undergo ASCT while on dialysis, a similar survival compared with the overall MM population has been reported. Therefore, for patients achieving remission following ASCT, kidney transplantation is an attractive option, offering an improved quality of life and significant economic advantage.

Method. This case series investigates the outcome of five patients who underwent an ASCT for MM with subsequent kidney transplantation between 2006 and 2012.

Results. Four patients presented with end-stage renal disease (ESRD) and one progressed to ESRD shortly after diagnosis. Induction chemotherapy regimens with novel agents including thalidomide and bortezomib were utilized. Following attainment of very good partial remission or complete remission, high-dose melphalan ASCTs were performed after a median of 10 months. Kidney transplantation (living donor $n = 3$, deceased donor $n = 2$) with tacrolimus-based immunosuppression regimens was completed at a median of 27 months after ASCT. Patients 1 and 3 experienced relapse of myeloma at 6 and 16 months after kidney transplantation. Patients 2, 4 and 5 remain alive at 55 months (median) after kidney transplantation with no evidence of relapse.

Conclusion. Forty percent of our cohort experienced a relapse in MM within 2 years of kidney transplantation. Death-censored graft survival and patient survival were 80% at 4 years. Our study adds to the growing literature supporting kidney transplantation following successful ASCT for MM and is useful when counselling patients regarding renal and haematological outcomes.

Keywords: autologous stem cell transplantation, kidney transplantation, multiple myeloma, outcome

INTRODUCTION

Multiple myeloma (MM) is the second most common haematological malignancy, accounting for 1% of all cancers [1].

Induction chemotherapy with novel anti-myeloma agents followed by high-dose melphalan autologous stem cell transplantation (ASCT) remains the gold standard of therapy for younger

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patients with MM and has led to significantly increased progression-free and overall survival [2].

End-stage renal disease (ESRD) has a substantial impact on morbidity and mortality [3]. Historically, patients with MM and ESRD had a 2.5 times higher relative risk of death relating to a higher tumour burden, lower tolerated chemotherapy doses and higher treatment-related mortality [4–6]. However, since the introduction of novel agents such as bortezomib, thalidomide and lenalidomide, there have been improvements in the rate of response even in patients with renal impairment [7, 8]. Furthermore, after ASCT, a similar survival for patients with ESRD compared with the overall MM population has been reported [1, 9].

Kidney transplantation improves survival compared with remaining on dialysis [5]. Previously, poor outcomes related to infection and disease progression in the context of immunosuppression were reported following kidney transplantation in patients with MM [10]. However, with current treatments and subsequent superior patient survival, successful kidney transplantation in patients with MM in remission is now possible [11].

MATERIALS AND METHODS

This case series reports on the risk of relapse of MM of five patients after kidney transplantation in King's College and Guys and St Thomas' Hospitals, London, UK, between 2006 and 2012. The patients were defined as having very good partial remission (VGPR) or complete remission (CR) in concordance with International Myeloma Working Group consensus criteria [12]. Clinical information and data were collected from medical records. Induction immunosuppression following kidney transplantation consisted of with two doses of basiliximab 20 mg on the day of the transplant and four days later. Maintenance immunosuppression included tacrolimus or ciclosporin with mycophenolate mofetil and prednisolone. This study was exempted from approval from an ethics' board.

RESULTS

Case reports

Three subjects were male and two were female. Median age at diagnosis of MM was 54 years (range 37–64). All patients were Caucasian. Median duration of follow-up from the time of kidney transplantation was 55 months (range 48–56). Results are summarized in Table 1 and Figure 1.

Patient 1. A 63-year-old male presented with ESRD related to cast nephropathy and immunoglobulin A (IgA) Kappa-related MM and was treated with thalidomide and dexamethasone inducing a VGPR followed by ASCT 25 months after diagnosis of MM. An ABO-incompatible living-related donor kidney transplant was performed 42 months later. Pre-transplant treatment with double filtration plasmapheresis and a single dose of rituximab 375/m² was administered to achieve anti-A1 titres of 1:8. MM relapse occurred 6 months after kidney transplantation and was treated with bortezomib, cyclophosphamide and dexamethasone (VCD) to CR. A second relapse, 32 months after the first relapse, was treated with bendamustine and dexamethasone. After the seventh cycle, he developed neutropenic sepsis related to H1N1 infection and chest infection with acute kidney injury requiring haemodialysis. Renal biopsy undertaken at this time demonstrated acute tubular necrosis with no evidence of

myeloma-related kidney disease or rejection (no donor-specific antibody was detected, C4d stains were negative). His kidney function recovered to an estimated glomerular filtration rate (eGFR) of 29 mL/min but unfortunately, he died from pneumonia at 55 months after kidney transplantation.

Patient 2. A 54-year-old male presented with ESRD related to lambda light chain myeloma and was treated with cyclophosphamide, thalidomide and dexamethasone (CTD) followed by VCD achieving CR. An ASCT was performed 10 months after CR and 33 months later he received a living donor kidney transplant. Two years after kidney transplantation, his eGFR was 61 mL/min. During a routine clinic visit, 28 months after transplantation, a reduction in eGFR to 40 mL/min was detected. Renal biopsy confirmed cellular rejection (Banff Type IIA [13]) and chronic antibody-mediated rejection [donor-specific antibody present to HLA A1 (MFI 1999), B8 (MFI 4071), B38 (MFI 1822), DQB1*06:03 (MFI 5619), C4d stains positive]. Despite treatment with intravenous methylprednisolone, his renal function continued to decline, and he started dialysis 53 months after transplantation. He remains in CR and is currently being assessed for re-transplantation.

Patient 3. A 37-year-old male presented IgG kappa myeloma and ESRD as a consequence of cast nephropathy. He was treated with CTD achieving VGPR followed by ASCT 11 months after diagnosis. He underwent living donor kidney transplantation 14 months after ASCT.

He suffered a relapse of MM 16 months after kidney transplantation and was treated with VCD chemotherapy, which was limited by peripheral neuropathy. Serum-free light chains (SFLC) concentrations decreased but the response was short-lived, and he then received lenalidomide and dexamethasone. This was stopped after 2 weeks despite reduction in SFLC due to renal graft dysfunction. A biopsy confirmed cellular rejection (Banff Type IIB [13]) with features of acute antibody-mediated rejection although C4d stain was negative and no donor-specific antibody was detected. He was treated with intravenous methylprednisolone and Ig and plasma exchange. Renal function improved (eGFR 27 mL/min). He received bendamustine and bortezomib and then CTD to a VGPR. He subsequently experienced a second relapse, 15 months after the first relapse in association with a decline in eGFR to 17 mL/min. Melphalan (25 mg/m²) and dexamethasone were commenced but not tolerated. Unfortunately, the patient experienced a myocardial infarction and cardiorespiratory arrest resulting in death at 48 months after kidney transplantation with a eGFR of 14 mL/min.

Patient 4. A 48-year-old female was diagnosed with a non-secretory Kappa light chain myeloma and cast nephropathy. Her eGFR was 15 mL/min, and she received thalidomide and dexamethasone to CR, followed by ASCT 10 months later. She developed ESRD 1 month after presentation with MM and underwent deceased donor kidney transplantation 27 months after ASCT. Her transplant function remained suboptimal and a biopsy confirmed cellular rejection (Banff Type IIA [13]), which was treated with intravenous methylprednisolone. A subsequent biopsy showed ongoing cellular rejection. A second course of intravenous methylprednisolone was administered and a further biopsy showed resolution of the rejection but evidence of calcineurin-inhibitor toxicity. Her eGFR at 1 year after transplantation was 15 mL/min, and she recommenced haemodialysis 24 months after transplantation. She is currently listed

Table 1. Demographics, clinical characteristics, MM treatment course and renal transplant outcomes

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Demographics					
Age (at time of diagnosis MM, years)	63	54	37	48	64
Sex	M	M	M	F	F
Ethnicity	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian
Timeline					
Date of diagnosis of MM and presentation of renal disease	December 2006	July 2010	March 2008	March 2011	March 2012
Time from MM diagnosis to ASCT (months)	25	10	11	10	10
Time from ASCT to kidney transplantation (months)	42	33	14	27	16
Time from MM diagnosis to kidney transplantation (months)	67	43	25	37	26
Time from kidney transplantation to relapse (months)	6	N/A	16	N/A	N/A
Date of death	February 2016	N/A	April 2014	N/A	N/A
Time of follow-up from kidney transplantation (months)	55	53	48	56	55
Details of MM					
Stage at diagnosis	Stage III ISS	Stage III ISS	Stage III ISS	Stage III ISS	Stage III ISS
SFLC at diagnosis (mg/L)	Not available at our hospital in 2006	Kappa 9.25 Lambda 23 400.00	Kappa 2150.00 Lambda 18.50	Kappa 3090.00 Lambda 18.10	Kappa 7.97 Lambda 163.00
Bone marrow biopsy	50% plasma cells, IgA Kappa	Ratio <0.01 90% plasma cells, Lambda Light	Ratio 116.22 80% plasma cells, IgG Kappa	Ratio 170.2 5% plasma cells, non-secretory	Ratio <0.01 90% plasma cells, Lambda Light
Chemotherapy pre-ASCT	TD × 6	Chain CTD × 1 VCD × 6	CTD × 6	TD × 6	CTD × 1 PAD × 2 CVTD × 6
Achieved VGPR/CR (months after diagnosis MM)	25	8	11	10	10
ASCT chemotherapy	HDM 100 mg/m ²	HDM 140 mg/m ²	HDM 140 mg/m ²	HDM 140 mg/m ²	HDM 140 mg/m ²
Details of relapse of MM					
First relapse of MM post ASCT (months)	48	No, remains in CR	30	No, remains in CR	No, remains in CR
First relapse of MM post kidney transplantation (months)	6	N/A	16	N/A	N/A
SFLC at first relapse (mg/L)	Kappa 1488.00 Lambda 0.63 Ratio 2361.9	N/A	Kappa 817.65 Lambda 16.89 Ratio 48.4	N/A	N/A
Bone marrow biopsy at first relapse	50% plasma cells	N/A	Not conducted	N/A	N/A
Chemotherapy for first relapse	VCD × 3	N/A	VCD × 5 lenalidomide/ dexamethasone bendamustine/bor- tezomib × 4	N/A	N/A
Haematological response achieved after treatment of first relapse	CR	N/A	CTD × 6 VGPR	N/A	N/A
Second relapse of MM post kidney transplantation (months)	38	N/A	31	N/A	N/A
SFLC at second relapse (mg/L)	Kappa 1464 Lambda 1.25 Ratio 1171.20	N/A	Kappa 683.24 Lambda 15.80 Ratio 43.2	N/A	N/A

(continued)

Table 1. (Continued)

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Bone marrow biopsy at second relapse	70% plasma cells	N/A	Not conducted	N/A	N/A
Chemotherapy for second relapse	Bendamustine/dexamethasone × 7	N/A	Melphalan	N/A	N/A
Adverse impacts of chemotherapy	No	No	Bortezomib – peripheral neuropathy	No	Bortezomib – peripheral neuropathy
Details of renal disease and transplantation	Yes	Yes	Yes	Yes	Yes
Renal involvement at presentation of MM	Cast nephropathy	Cast nephropathy	Cast nephropathy	Cast nephropathy	Cast nephropathy
Renal biopsy results	Cast nephropathy	Cast nephropathy and tubule-interstitial nephritis	Cast nephropathy	Cast nephropathy	Cast nephropathy
Type of renal allograft	ABO-incompatible, live related	Live unrelated	Live related	Deceased DBD	Deceased DBD
HLA mismatch	1-2-1	1-2-1	1-1-1	0-0-0	1-1-0
Induction immunosuppression	(Pre-transplant: 5 × sessions of double filtration plasmapheresis Rituximab 375 mg/m ²) Basiliximab	Basiliximab	Basiliximab	Basiliximab	Basiliximab
Maintenance immunosuppression	Tacrolimus, MMF and prednisolone	Tacrolimus, MMF and prednisolone	Ciclosporin, MMF and prednisolone	Tacrolimus, MMF and prednisolone	Tacrolimus, MMF and prednisolone
eGFR (mL/min) at:					
1 year	78	63	43	15	35
2 years	76	61	38	Haemodialysis	38
Last follow-up	29	Haemodialysis	14	Haemodialysis	27
UPCR (mg/mmol) at:					
Pre-transplant	13	19	Not tested	Not tested	Not tested
1 year	15	13	11	Not tested	Not tested
2 years	48	20	35	Not tested	Not tested

DBD, donation after brain death; F, female; M, male; ISS, International Staging System; HDM, high-dose melphalan; N/A, not applicable; MMF, mycophenolate mofetil; TD, thalidomide/dexamethasone.

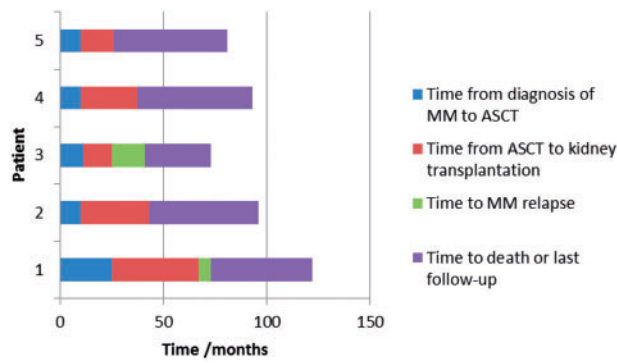


FIGURE 1: Timeline of diagnosis of MM to last follow-up.

for further renal transplantation but remains in CR 56 months after kidney transplantation.

Patient 5. A 64-year-old female presented with Lambda light chain myeloma and cast nephropathy requiring dialysis. She was treated with bortezomib, adriamycin and dexamethasone (PAD), cyclophosphamide, bortezomib and thalidomide (CVTD) followed by CTD as she developed bortezomib-related peripheral neuropathy. She achieved a VGPR and underwent ASCT 10 months after diagnosis of MM and then deceased donor kidney transplantation 166 months after ACST. Her eGFR is 27 mL/min at 55 months after kidney transplantation and she remains in CR.

DISCUSSION

This study describes the outcome of patients who underwent kidney transplantation following ASCT for MM. ASCTs for MM were performed after a median of 10 months (range 10–25) following diagnosis of MM. Kidney transplantation was performed at a median of 27 months after ASCT (range 16–42). Three patients did not experience relapse of MM with median follow-up period of 55 months (range 53–56) after kidney transplantation. Two patients experienced relapse of myeloma at a median of 11 months after kidney transplantation. These two patients died at a median of 52 months after kidney transplantation. Patient 1 received an ABO-incompatible transplant and therefore received additional immunosuppressive treatment with plasmapheresis and rituximab. It is conceivable that this contributed to the early relapse of MM. However, this relapse was successfully treated to CR and the patient developed a second relapse 38 months after kidney transplantation. The first relapse for Patient 3 was also treated to VGPR and he remained in remission for a further 15 months. Both patients died with a functioning renal transplant at a median of 52 months after transplantation.

For the two of the three patients who remain in CR, the transplant failed at a median of 39 months after transplantation. Graft loss in both cases was attributed to rejection. Of note, treatment of the rejection episodes was not de-escalated due to the history of MM.

This case series report contributes to the small number of case series that have previously been reported in patients with MM treated with contemporary chemotherapeutic regimens with successful outcomes following kidney transplantation (Table 2). Lum et al. reported on two patients who received

bortezomib-based treatments and continued with fortnightly bortezomib after kidney transplantation [10]. Induction immunosuppression for kidney transplantation consisted of basiliximab, similar to our patient cohort. At 25 and 13 months, both patients remain in remission with serum creatinine of 1–2 mg/dL. Hassoun et al. reported on two patients treated with thalidomide, dexamethasone, melphalan and doxorubicin followed by ASCT and kidney transplantation 14.1 and 45.7 months after achieving CR [14]. At 21.8 and 24.1 months, respectively, both patients remain in remission with functioning renal allografts. Sánchez Quintana et al. reported on two patients treated with lenalidomide followed by ASCT and then kidney transplantation [15]. At 48 and 36 months, both patients remain in remission with functioning renal allografts. Le et al. reported on four patients treated with bortezomib, lenalidomide, cyclophosphamide and thalidomide followed by ASCT and then kidney transplantation at between 20 and 66 months after remission [16]. At between 16 and 58 months of follow-up, the patients have an eGFR of 59–73 mL/min. Two patients continued with maintenance therapy of lenalidomide or bortezomib and one patient relapsed but was treated successfully with carfilzomib, cyclophosphamide and dexamethasone. It is interesting to note that the patient who relapsed received antithymocyte induction in the context of ABO-incompatible transplantation. In summary for these case series, the median time to transplant from remission was 39 months and median follow-up after transplantation was 31 months. Only one patient suffered with a relapse but that was treated successfully to CR. Patient and kidney transplant survival was 100% with no episodes of rejection reported. One patient developed BK viraemia necessitating a reduction in immunosuppression.

In comparison with the published case series, our patients were transplanted 12 months earlier after ASCT and we have follow-up data for a further 21 months. In this study, all the patients had renal disease attributable to cast nephropathy and received an ASCT. The only patient that experienced relapse of MM also received intensive induction immunosuppression for an ABO-incompatible transplant. In our case series, the relapse rate was increased with inferior patient and graft survival compared with previous cases. Our 4-year death-censored graft survival was 80% and 4-year patient survival after transplantation was 80%. Of note, our patients did not receive maintenance chemotherapy after kidney transplantation, and our patients had longer follow-up, and these factors may account for the differences observed.

Treatment of relapsed myeloma remains challenging. In our series, both patients were treated effectively for the first relapse resulting in disease-free interval of 24 months (median). However, treatment of the second relapse was not successful. Patient 3 was treated with lenalidomide, which can precipitate kidney transplant rejection [17, 18], and therefore perhaps these agents should be avoided. However, others have reported maintenance as well as treatment for relapse with lenalidomide without adverse impact to the transplant kidney (Table 2). In addition, sepsis is the second most common cause of death following kidney transplantation [19]. Relapse of myeloma confers an additional risk of sepsis related to immunoparesis and chemotherapy. Careful consideration of immunosuppression regimens and immunological risk of the transplant, to avoid sepsis and minimize the risk of kidney transplant rejection, is imperative.

The main limitation of our study is the small number of patients and therefore caution must be applied when considering the relapse rate and graft outcome data. However, the

Table 2. Published case reports of renal transplantation in patients treated with autologous stem cell transplantation for multiple myeloma

Reference	Patient demographics	Native kidney biopsy	MM treatment	Time to kidney transplant after remission (months)	Type of kidney transplant and immunosuppression	Last follow-up after kidney transplant (months)	Haematological response at last follow-up	eGFR at last follow-up (mL/min)
Lum <i>et al.</i> [10]	67-year-old male	No biopsy but renal disease thought to be hypertensive nephrosclerosis.	Dexamethasone/bortezomib; bortezomib maintenance	12	Living unrelated transplant with basiliximab induction and maintenance with tacrolimus, mycophenolic acid and prednisolone and then ciclosporin and prednisolone (due to BK viraemia)	25	CR	34
	62-year-old female	Cast nephropathy	Plasmapheresis; dexamethasone/bortezomib; bortezomib maintenance	24	Living unrelated transplant with basiliximab induction and maintenance with tacrolimus and prednisolone	13	CR	60
Hassoun <i>et al.</i> [13]	42-year-old male	LCDD	Thalidomide/dexamethasone; dexamethasone; melphalan/dexamethasone/doxorubicin/dexamethasone; cyclophosphamide mobilization; melphalan conditioning; ASCT	14	No details given	22	CR	Normal
	51-year-old female	LCDD	Thalidomide/dexamethasone; dexamethasone; melphalan/dexamethasone/doxorubicin/dexamethasone; cyclophosphamide mobilization; melphalan conditioning; ASCT	46	No details given	24	CR	Normal
Sánchez Quintana <i>et al.</i> [14]	38-year-old male	LCDD	Dexamethasone; ASCT; lenalidomide maintenance	48	Deceased donor transplantation (DBD); no induction details given; maintenance with tacrolimus and prednisolone	48	CR	Not given
	44-year-old female	No biopsy	Vincristine/adriamycin/dexamethasone; ASCT; maintenance with thalidomide then lenalidomide	48	Deceased donor transplantation (DBD); no induction details given; maintenance with tacrolimus and prednisolone	36	VGPR	Not given

(continued)

Table 2. (Continued)

Reference	Patient demographics	Native kidney biopsy	MM treatment	Time to kidney transplant after remission (months)	Type of kidney transplant and immunosuppression	Last follow-up after kidney transplant (months)	Haematological response at last follow-up	eGFR at last follow-up (mL/min)
Le et al. [15]	52-year-old male	LCDL with cryoglobulinaemic GN	Plasmapheresis, thalidomide/dexamethasone; vincristine/doxil/dexamethasone; cyclophosphamide mobilization; melphalan conditioning then ASCT	66	No details given	58	CR	73
	50-year-old male	No biopsy	Bortezomib/dexamethasone; lenalidomide/doxorubicin/cyclophosphamide/dexamethasone; melphalan conditioning then ASCT lenalidamide followed by bortezomib maintenance; lenalidomide/dexamethasone (progression); carfilzomid/cyclophosphamide/dexamethasone; pomalidomide/cyclophosphamide/dexamethasone	20	ABO-incompatible kidney transplant with antithymocyte globulin induction	48	SD	59
	50-year-old male	LCDL	Bortezomib/dexamethasone/lenalidomide; melphalan conditioning then ASCT; lenalidomide, then bortezomib maintenance	32	No transplant details given; no induction details given; maintenance with tacrolimus, mycophenolic acid and prednisolone	43	CR	59
	47-year-old male	No biopsy	Bortezomib/dexamethasone/lenalidomide; cyclophosphamide mobilization; melphalan conditioning then ASCT; lenalidamide maintenance	53	No transplant details given with basiliximab induction and maintenance with tacrolimus and mycophenolic acid	16	CR	60

SD, stable disease; LCDL, light chain deposition disease; DBD, donation after brain death; GN, glomerulonephropathy.

strength is the length of follow-up. Our study supports kidney transplantation as the preferred treatment for ESRD following successful ASCT for MM and is useful when counselling patients regarding outcomes following kidney transplantation after MM. Furthermore, there are emerging novel agents that are suitable to be employed in ESRD which may improve the depth of response prior to transplant and can be employed to treat relapse following transplantation.

European Best Practice Guidelines advise a waiting period of 2 years between successful induction treatment and renal transplantation [20]. In the future, it may be possible to risk-stratify and select a subgroup of patients with myeloma who are predicted to have a deep response following ASCT [12], and these patients with a better prognosis could be considered for earlier kidney transplantation. However, further evidence is needed to support this [21]. Uncertainty remains around the role of continuing chemotherapy after kidney transplantation to prevent relapse and the optimal treatment of relapsed MM.

We have presented a case series of five patients submitted for renal transplantation after ASCT and CR of MM and demonstrated that 40% of our cohort experienced a relapse in MM within 2 years of kidney transplantation. Death-censored graft survival and patient survival was 80% at 4 years. From our experience, we suggest avoiding transplantation from donors, which would require intensive immunosuppression and immunomodulatory chemotherapy agents to reduce the risk of MM relapse and renal rejection.

CONFLICT OF INTEREST STATEMENT

No disclosures or conflicts of interest for all authors. The results presented in this article have not been published previously in whole or part, except in abstract format.

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