Kidney Transplant in Multiple Myeloma

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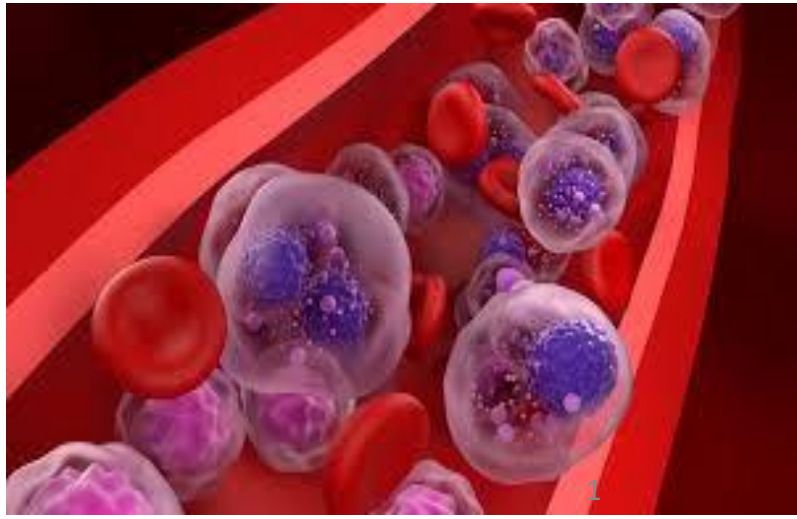


Introduction

- (MM) is a neoplastic proliferation of plasma cells in the bone marrow resulting in abnormal production of monoclonal immunoglobins leading to anemia, hypercalcemia, osteolytic bone lesions, and commonly renal impairment.
- Historically, individuals with MM and end stage renal disease (ESRD) were not considered candidates for kidney transplantation due to concerns for their overall poor prognosis, risk of disease recurrence, and increased risk of infection.
- However over the past 15 years, the survival of MM has greatly increased with the advent of an array of effective drugs and autologous stem cell transplantation (SCT).

MM AND KIDNEY DISEASE

- Renal involvement is common in patients with MM with about 25% of patients having renal impairment at time of presentation and 50% developing kidney disease during the course of their disease.
- These patients can present with several patterns of injury including CN, MIDD, or amyloidosis.
- Cast nephropathy is the most common pattern occurring in 40-63% of myeloma patients with renal involvement.
- Monoclonal immunoglobulin deposition disease occurs in 19% to 26% of patients with renal involvement and 7% to 30% will have amyloid kidney involvement.

Renal manifestations of multiple myeloma

Glomerular lesions

Tubular lesions

Hypercalcemia

Thrombotic microangiopathy

Amyloidosis

Monoclonal immunoglobulin deposition disease

Membranoproliferative glomerulonephritis

Fibrillary glomerulonephritis and immunotactoid glomerulopathy

Collapsing FGSS (bisphosphonates)

C3 glomerulopathy

Light chain cast nephropath

Fanconi syndrome

Interstitial nephritis

MM AND KIDNEY DISEASE

- Cast nephropathy is recognized by highly refractile proteinaceous casts in the renal tubules which are usually associated with significant tubular inflammation.
- The mechanism of cast formation is due to the precipitation of filtered LC proteins with Tamm-Horsfall protein resulting in obstruction of the distal tubular lumen and reactive inflammation.
- In MIDD, monoclonal immunoglobulins are deposited in the kidney along the glomerular and tubular basement membranes, leading to proteinuria and progressive CKD.

MM AND KIDNEY DISEASE

- Despite these advances, subsets of patients with high-risk disease do not enjoy long-term survival.
- Many systems exist to classify patients as having high risk versus other, but the majority incorporate genetic markers; fluorescence in situ hybridization or gene expression profiling.
- Patients with high-risk disease have a greater likelihood of early relapse and disease progression.
- In general, patients with high-risk MM can be expected to have a survival of less than 5 years, with a prominent component of mortality being present during the first 2 years after diagnosis.

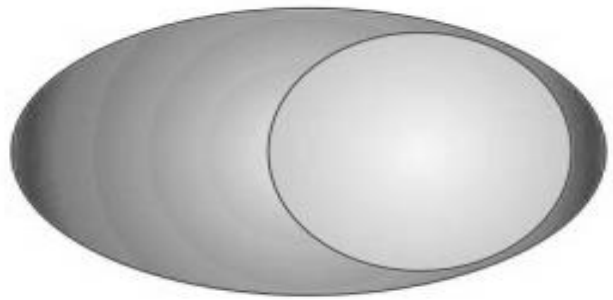
New treatment in MM

- There are 3 new main groups of drugs used for the treatment of myeloma; proteasome inhibitors (PIs), immunomodulatory drugs (IMIDs) and monoclonal antibodies .
- PIs (bortezomib, carfilzomib, ixazomib, and other drugs in development) revolutionized the treatment of myeloma by creating endoplasmic reticulum stress and apoptosis due to the high rate of production of immunoglobulin molecules by myeloma cells.
- Immunomodulatory drugs are drugs derived from thalidomide and include lenalidomide, pomalidomide, and others in development.
- Immunomodulatory drugs are oral agents that can be used over an extended period because of their tolerance profile and have been used successfully in combination and as part of maintenance after SCT.
- Both IMIDs and PIs are interesting in that they target the normal biology of plasma cells, a biology that is retained in the clonal plasma cells, and one that creates cell vulnerabilities. Immunomodulatory drugs are pleiotropic in their mechanism of action but contain an immune stimulant component that will be of relevance as one considers these drugs in the setting of organ transplantation.

New treatment in MM

- Another class of drugs includes the monoclonal antibodies, some target CD38 (daratumumab and isatuximab)19 and others target SLAMF7 (elotuzumab).
- Daratumumab has direct cytotoxic activity against myeloma cells and has been used alone or in combination.
- Elotuzumab has no single-agent activity and has been used mostly in combination with lenalidomide and dexamethasone.
- Lastly, corticosteroids are almost always used as part of combinations used for the treatment of myeloma because they are cytotoxic to plasma cells and increase antimyeloma activity of most drugs.

Mechanism of action of myeloma drugs



IMIDs
Thalidomide, lenalidomide and pomalidomide
MOA: Via cereblon (CRBN) degrades IKZF1/3 and also promote oxidative stress via protein metabolism. Pleomorphic including immune activation.

PROTEASOME INHIBITORS
Bortezomib, carfilzomib, ixazomib, oprozomib and marizomib
MOA: ER stress induced by altered protein metabolism

HISTONE DEACETYLASE INHIBITORS
Panobinostat
MOA: Potentiate ER stress induced by proteasome inhibitors

SLAMF7 MONOCLONAL ANTIBODIES
Elotuzumab
MOA: Triggers NK cell response when used in conjunctions with IMIDs

CORTICOSTEROIDS
Dexamethasone, prednisone, others
MOA: Via steroid receptor induce apoptosis and disrupt thioredoxin.

ALKYLATORS AND OTHER CHEMOTHERAPY AGENTS
Melphalan, cyclophosphamide and bendamustine
MOA: Classic chemotherapy drugs that cause DNA damage. Used for SCT

ANTI-CD38 ANTIBODIES
Daratumumab, isatuximab
MOA: Antibody mediated cell killing plus other immune effects (pleomorphic)

FIGURE 1. This figure shows the various mechanisms of action of the medications used in the treatment of MM. MOA, mechanism of action; IKZF1/3, names for the genes Ikaros and Aiolos; ER, endoplasmic reticulum.

Kidney transplant after chemotherapy for MM

Reference	No. patients	Pretransplant chemotherapy	Kidney lesion	Outcomes
Humphrey 1975 [21]	1 MM	cyclophosphamide		DDKTx, Died 15 mo post-aspergillosis, DDKTx without recurrent MM
Cosio 1981 [22]	1 MM	Mephalan, prednisone		DDKTx, no recurrence at 18 mo
De lima 1981 [23]	1 MM	Mephalan, prednisone	NR	DDKTx. Recurrent MM 3 mo, died 11 mo sepsis
Walker 1983 [24]	1 MM	Mephalan, prednisone	NR	MM in remission, DKTx, No recurrence, alive 4.5 y
Iggo 1989 [25]	2 MM	Mephalan, prednisone	NR	DDKTx. 1 relapsed 6 mo and died 17 mo. 1 died 1 mo sepsis and MM.
Dagher 1996 [26]	1 MM	Not treated		Alive with good creatinine 48 mo
Van Bommel 1996 [27]	9 MM (review includes Iggo)	Not reported	NR	3 died MM, 3 died infection, 3 alive without recurrence 18, 18 and 54 mo
Lum 2017 [28]	2 MM	Bortezomib, dexamethasone	CN	2 LDKTx while in PR. Stable at 13 and 25 mo. Remain on Bortezomib

KTx, kidney transplant; DDKTx, deceased donor kidney transplant; LDKTx, living donor kidney transplant; NR, not reported.

CURRENT RECOMMENDATIONS FOR KIDNEY TRANSPLANTATION IN PATIENTS WITH MM

- Determining patients according to their genetic risk category seems to be the best, albeit imperfect, method to select individuals with a greater likelihood of long-term survivorship and transplant value.
- Nevertheless, genetic factors alone can only explain a fraction of the heterogeneity of outcomes.
- A new arbitrary system that further enhances this discriminatory process would seem to be warranted for better selecting patients.

CURRENT RECOMMENDATIONS FOR KIDNEY TRANSPLANTATION IN PATIENTS WITH MM

- In addition to these aforementioned genetic factors, other factors can help identify individuals with a high risk of rapid progression and include :
- high lactate dehydrogenase,
- presence of extramedullary disease,
- poor performance status,
- persistent disease post-SCT in positron emission tomography imaging,
- rapid relapse.
- The greatest conundrum is how long to make this period of relapse-free survival to maximize benefit.

CURRENT RECOMMENDATIONS FOR KIDNEY TRANSPLANTATION IN PATIENTS WITH MM

- A novel approach to gauge the progress of initial treatment for MM is the use of **minimal residual disease (MRD**) measurements of the bone marrow.
- Methods to do so include flow cytometry, polymerase chain reaction and next-generation sequencing.
- While there is no universally accepted threshold most believe a level of at least of 10−5 is desirable and preferable at 10−6.
- One could postulate that achievement of MRD-negative status could be used as a selection criteria for renal transplant candidates.

CURRENT RECOMMENDATIONS FOR KIDNEY TRANSPLANTATION IN PATIENTS WITH MM

- Likewise, patients who have high-risk markers and who do not achieve MRD-negative status are at high risk of early relapse and thus would be premature to recommend kidney transplantation to them.

- **It is possible that MRD determinations will need to be done longitudinally in those receiving a kidney transplant to monitor the depth of responses.**

CURRENT RECOMMENDATIONS FOR KIDNEY TRANSPLANTATION IN PATIENTS WITH MM

- One therapeutic option that has greatly improved survival of MM is maintenance therapy post-SCT.
- Several randomized studies show that **lenalidomide** improves progression-free survival, and one study showed an improvement in overall survival.

CURRENT RECOMMENDATIONS FOR KIDNEY TRANSPLANTATION IN PATIENTS WITH MM

- One option to avoid IMIDs, at least earlier in the course after kidney transplant, could be to use other drugs previously explored as maintenance for MM.
- These drugs could include **bortezomib**, ixazomib and daratumumab.

CURRENT RECOMMENDATIONS FOR KIDNEY TRANSPLANTATION IN PATIENTS WITH MM

- Patients who have MM and kidney transplantation should be monitored carefully with close interaction between the transplant team and the hematologist.

- They should have **free LCs** and **serum protein electrophoresis** checked at a minimum of **every 3 months** with the caveat that they may need more frequent monitoring if there is a recurrence and treatment is being initiated.

- In addition, many of the drugs used to treat MM can have immunosuppressive effects and interact with transplant related medications so a multidisciplinary approach is essential.

CURRENT RECOMMENDATIONS FOR KIDNEY TRANSPLANTATION IN PATIENTS WITH MM

- Over time, many myeloma regimens can produce profound hypogammaglobulinemia, also a consideration for a patient who is already receiving immuno- suppression and is at an increased risk of infection.
- For individuals on MM therapy, appropriate infection prophylaxis should be initiated as recommend by hematology.

Conclusion

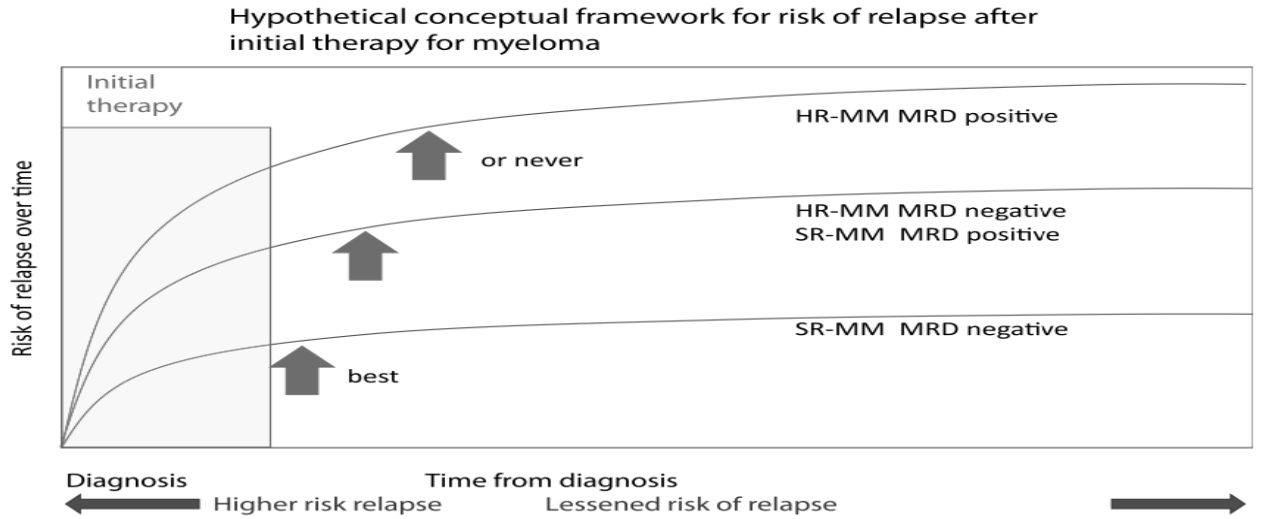


FIGURE 2. In this figure, we show the conceptual framework upon which one could make decisions about when to offer kidney transplantation. We have arbitrarily divided patients with MM into 3 groups. Patients who have standard-risk disease and that have achieved excellent levels of response, as determined by having a negative test in an MRD-negative assay. These patients could be considered after 6 months after initial antimyeloma therapy (including SCT) for renal transplantation. At the other end of the spectrum, we see patients with high-risk myeloma that still have evidence of residual disease, and as a group they are least likely to benefit from kidney transplantation given their shorter survival. Renal transplantation should be considered carefully, and in our opinion only after it is clear that the disease has been well controlled, and that the response is durable. In between are patients who have either high-risk disease and negative MRD assays, or patients who have standard risk disease but remain positive for MRD, but that otherwise had no evidence of overt disease. These patients could be considered for renal transplant after 12 months of therapy. HR-MM, high-risk MM; SR-MM, standard-risk MM.

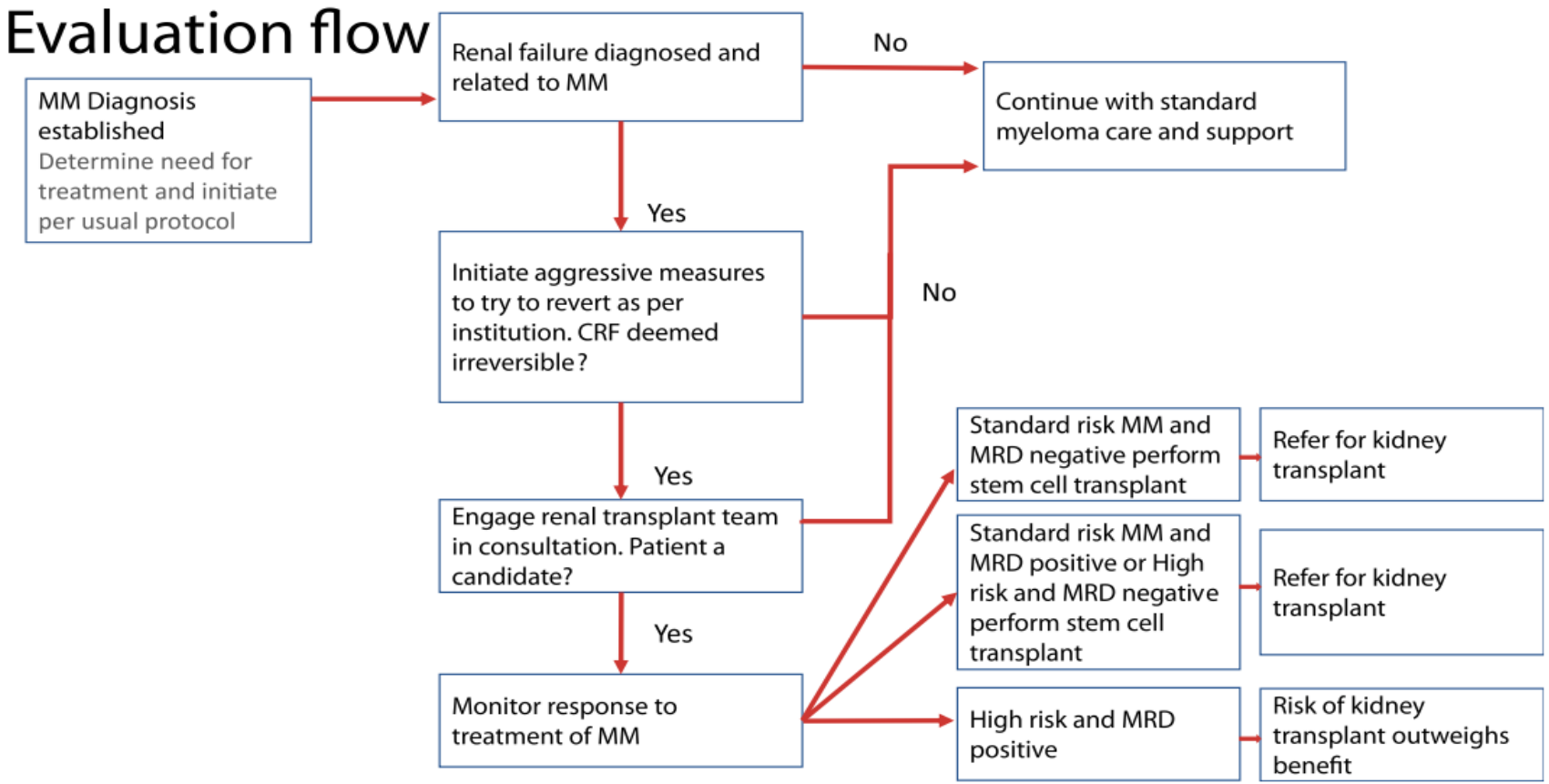
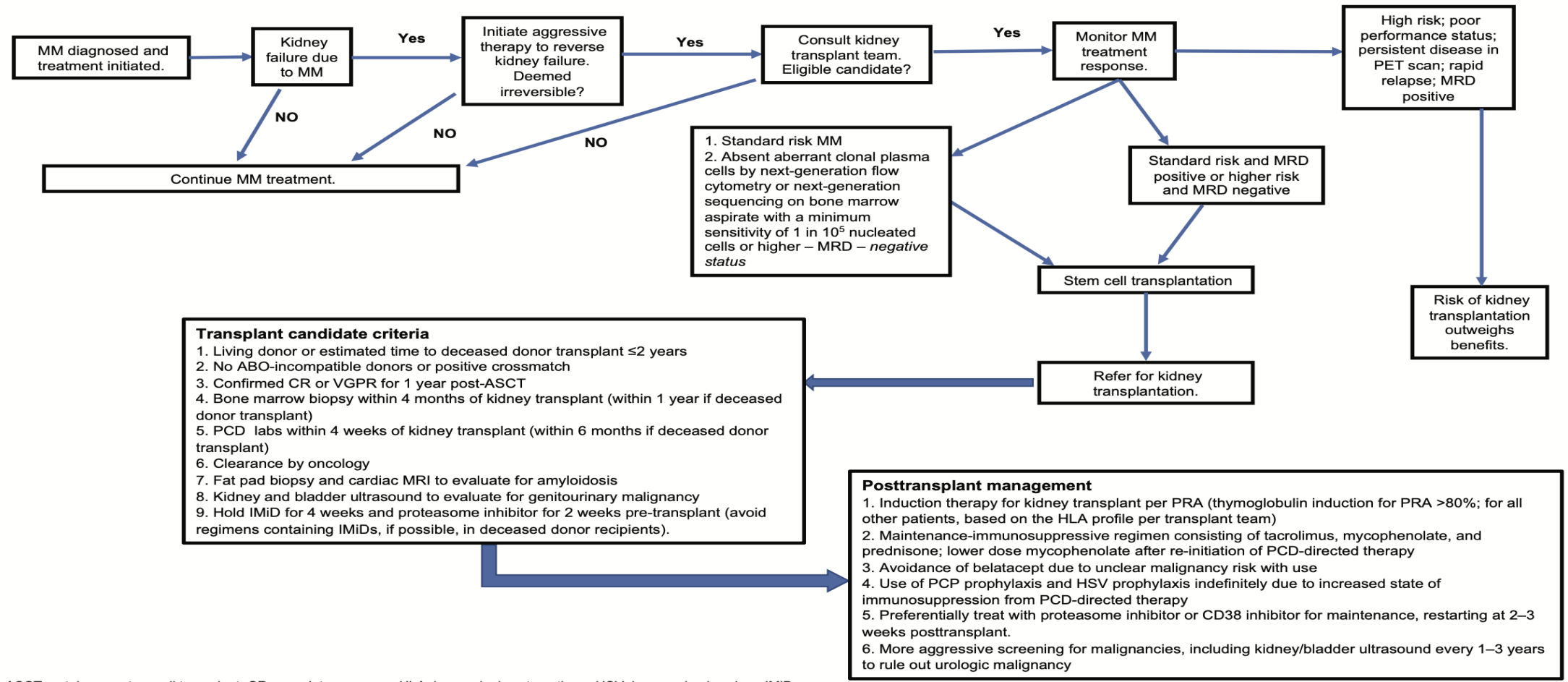


FIGURE 3. This figure is a schematic representation of the process for individuals with MM and chronic renal failure. Transplant nephrology should be consulted for individuals with irreversible renal disease to determine their candidacy for kidney transplant. If it is felt that the patient is a candidate for kidney transplant then MM treatment should pursued which should include SCT before renal transplantation. Individuals with high-risk disease should not be considered for kidney transplant as the risk outweighs the benefit. CRF, chronic renal failure.

Figure 1. Proposed evaluation of multiple myeloma patient and kidney failure and follow-up



ASCT, autologous stem cell transplant; CR, complete response; HLA, human leukocyte antigen; HSV, herpes simplex virus; IMiD, immunomodulatory drug; MM, multiple myeloma; MRD, minimal residual disease negative status; MRI, magnetic resonance

Posttransplant management

1. Induction therapy for kidney transplant per PRA (thymoglobulin induction for PRA >80%; for all other patients, based on the HLA profile per transplant team)
2. Maintenance-immunosuppressive regimen consisting of tacrolimus, mycophenolate, and prednisone; lower dose mycophenolate after re-initiation of PCD-directed therapy
3. Avoidance of belatacept due to unclear malignancy risk with use
4. Use of PCP prophylaxis and HSV prophylaxis indefinitely due to increased state of immunosuppression from PCD-directed therapy
5. Preferentially treat with proteasome inhibitor or CD38 inhibitor for maintenance, restarting at 2–3 weeks posttransplant.
6. More aggressive screening for malignancies, including kidney/bladder ultrasound every 1–3 years to rule out urologic malignancy

Review

Kidney Transplant in the Era of Modern Therapy for Multiple Myeloma

Janna L. Huskey, MD,[1] Raymond L. Heilman, MD,[1] Hasan Khamash, MD,[1] and Rafael Fonseca, MD[1]

Abstract: Chronic kidney disease is common in patients with multiple myeloma. Historically, individuals with end-stage renal disease and multiple myeloma did poorly with renal transplantation due to higher mortality rates from the malignancy itself or associated comorbidities. However, over the past 2 decades, there have been significant advances in the treatment of multiple myeloma with the advent of new therapeutic agents resulting in an improvement of long-term survival. As a result, more individuals with multiple myeloma are being referred for kidney transplantation, especially those with good functional capacity and minimal comorbidities. Recent literature has suggested that certain patients with multiple myeloma can successfully undergo renal transplantation after stem transplantation with consideration for maintenance therapy, although caution should be used with immunomodulating drugs due to the anecdotally reported risk of acute rejection. Therefore, having a multidisciplinary approach with the transplant team and hematology both before and after transplant is crucial in maximizing the chance of success for these individuals. This review summarizes the literature on renal transplantation in patients with multiple myeloma as well as the therapeutic advancements that have occurred which may allow certain patients to undergo successful transplantation.

(*Transplantation* 2018;102: 1994–2001)

Multiple myeloma (MM) is a neoplastic proliferation of plasma cells in the bone marrow resulting in abnormal production of monoclonal immunoglobins leading to anemia, hypercalcemia, osteolytic bone lesions, and commonly renal impairment. Historically, individuals with MM and end stage renal disease (ESRD) were not considered candidates for kidney transplantation due to concerns for their overall poor prognosis, risk of disease recurrence, and increased risk of infection. However over the past 15 years, the survival of MM has greatly increased with the advent of an array of effective drugs and autologous stem cell transplantation (SCT). There have also been advances in the management of kidney transplant recipients, making it reasonable to consider these patients for transplantation. The goal of this review is to discuss the outcome of kidney transplantation in patients with advanced chronic kidney disease (CD) due to MM. In addition, we will review the advancement in therapy for MM over the years which has led to an improvement in patient survival. We will focus our discussion to MM patients with CKD related to cast nephropathy (CN) or monoclonal Ig kidney deposition disease (MIDD).

MM AND KIDNEY DISEASE

Renal involvement is common in patients with MM with about 25% of patients having renal impairment at time of presentation and 50% developing kidney disease during the course of their disease.[1] These patients can present with several patterns of injury including CN, MIDD, or amyloidosis. Cast nephropathy is the most common pattern occurring in 40-63%

Kidney Transplantation

OPEN

Kidney Transplantation in Patients With Active Multiple Myeloma: Case Reports

Erik Lawrence Lum, MD,[1] Neil Kogut, MD,[2] Thu Pham, MD,[1] Gabriel M. Danovitch, MD,[1] and Suphamai Bunnapradist, MD[1]

Should a Kidney Transplant Be Performed in a Patient with Multiple Myeloma?

By Jaya Kala

Kidney injury and kidney failure are frequently found in patients with multiple myeloma. With the introduction of novel agents in the last two decades, the outcome of patients with multiple myeloma has tremendously improved. The median survival has reached 7.7 years for patients under the age of 65 years (1). Despite the advances in therapies, patients continue to develop end stage kidney disease (ESKD). The survival of myeloma patients on dialysis is inferior to those without myeloma. Because of poor prognosis of multiple myeloma, kidney transplantation has not been considered an option (2). However, with evolving therapies for multiple myeloma, which

After kidney transplant with 28 living donors and 23 deceased donors, relapse of multiple myeloma was seen in 50% (29 of 58) and graft loss in approximately 25% (15 of 58), and approximately 32% (19 of 58) died. The wait period for kidney transplant varied from 4 months before to 13 years after remission. As a result of the rapidly changing treatment landscape, the regimens used varied significantly among the patients. The cytogenetic risk and minimal residual disease status were unknown in these patients.

Because of the low number of patients analyzed and significant heterogenicity between studies, no clear conclusion about factors impacting recurrence, death

transplant team and hematology both before and after transplant are crucial to maximize the chances of success for these individuals and maximize years gained from transplanted organs. With an ever-expanding wait list, organ shortage, and prolonged wait times, careful consideration of transplant candidates must be made. ■

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Kidney Transplant Outcomes of Patients With Multiple Myeloma

Cihan Heybeli[1], Andrew J. Bentall[2], Mariam Priya Alexander[3], Hatem Amer[2], Francis K. Buadi[4], Angela Dispenzieri[4], David Dingli[4], Morie A. Gertz[4], Naim Issa[2], Prashant Kapoor[4], Aleksandra Kukla[2], Shaji Kumar[4], Elizabeth C. Lorenz[2], S. Vincent Rajkumar[4], Carrie A. Schinstock[2] and Nelson Leung[2,4]

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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

Table 1. Published reports of outcomes of multiple myeloma patients after kidney transplantation

Reference	Patients, No.	Follow-up, month	Myeloma Rx pre-KTx	Hematological response pre-KTx	Maintenance treatment for MM	Remission to KTx, month	KTx induction	KTx donor type	Relapse of MM, No.	Death, No.	Graft loss, No.
Le et al. (7)	4	16–58	4 Chemo + SCT	1 VGPR, 3 CR	2 Bortezomib 2 None	20–66	No data	No data	1	0	0
Lum et al. (8)	2	13–25	2 Chemo	1 CR, 1 active	2 Bortezomib	12, 0	Basiliximab	2 Living	0	0	0
Shah et al. (9)	5	48–56	5 Chemo + SCT	3 VGPR, 2 CR	No data	14–166	No data	3 Living 2 DBD	3	2	3
Huskey et al. (10)	4	10–72	1 Chemo, 3 Chemo + SCT	3 VGPR, 2 CR	2 Lenalidomide 1 Bortezomib	–4 to –36	2 Basiliximab 2 Alemtuzumab	2 Living 2 DBD	4	1	2
Hedvat et al. (11)	3	36–47	3 Chemo + SCT	No data	No data	20–46	No data	No data	1	1	1
Kormann et al. (2)	13	51.7	8 Chemo + SCT, 3 Chemo	13 VGPR/CR	No data	39–159	3 ATG 10 Basiliximab	2 Living 11 DBD	7	5	6
Heybeli et al. (1)	12	40	6 Chemo + SCT, 6 Chemo	8 CR. 2 VGPR, 2 PR	3 Lenalidomide	6–60	4 ATG 8 Basiliximab	2 Living 11 DBD	9	5	3
Dinh et al. (6)	10	44	10 Chemo + SCT	1 VGPR, 9 CR	3 Bortezomib 1 Lenalidomide 2 Daratumumab 1 Carfilzomib 0 None	7–66	4 ATG 6 Basiliximab	8 Living 2 DBD	3	3	0
Leung et al. (12)	1	92	Chemo	No data	No data	No data	No data	Living	1	1	0
Sánchez Quintana et al. (13)	2	48	2 Chemo + SCT	1 CR 1 VGPR	2 Lenalidomide	48	No data	2 DBD	0	0	0
Domínguez-Pimentel et al. (14)	1	98	Chemo + SCT	No data	Lenalidomide	30	Basiliximab	DBD	0	1	0
Beitinjaneh et al. (15)	1	60	Chemo + SCT	CR	None	36	No data	Living	0	0	0
Total	**58**	**10–98**	**43 Chemo + SCT, 13 Chemo**	**27 CR, 21 VGPR, 3 PR, 2 Active**	**8 Bortezomib 9 Lenalidomide 2 Daratumumab 1 Carfilzomib**	**–4 (KTx before CR) to 166**	**28 Basiliximab 2 Alemtuzumab 11 ATG**	**28 Living 23 DBD**	**29**	**19**	**15**

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.

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.

Thanks for attention