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Editorial Comment

EDITORIAL COMMENT

Multiple myeloma and kidney transplantation: the beginning of a new era

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ABSTRACT

The introduction of several novel therapeutic agents has improved the outcome in multiple myeloma (MM) patients including those with chronic kidney disease, and it is predicted that MM will become a curable disease in a substantial subset of MM patients. While in the past—because of inferior posttransplant outcomes—renal transplantation was not offered to MM patients, recent data suggest that renal transplantation is a viable treatment option in patients treated with modern anti-myeloma induction therapy followed by autologous stem cell transplantation achieving durable complete responses. The article of Shah, Ibrahim, Delaney *et al.* [Risk of relapse of multiple myeloma following kidney transplantation: a case series report. *Clin Kidney J* 2018 (in this issue)] in the current issue of *Clinical Kidney Journal* adds to this evidence and highlights the limitations and outstanding questions concerning renal transplantation in MM patients.

Keywords: allograft survival, complications, immunomodulatory drugs, multiple myeloma, renal transplantation

Over the past two decades, 11 new drugs have become available for the treatment of multiple myeloma (MM), and their usage has resulted in the average survival of MM patients increasing from 29 months in 1998 to >8 years today [1]. Moreover, while MM was considered an incurable disease in the past, optimal treatment consisting of anti-myeloma induction therapy followed by autologous stem cell transplantation (ASCT) and maintenance therapy is estimated to result in prolonged disease-free remission in 20%. The achievement of complete remission is associated with a 30% chance of non-progression in the following 20 years [2].

MM is associated with different renal manifestations and chronic kidney disease (CKD) is a common complication of MM: renal impairment is present at the time of diagnosis or will develop during the disease course in 25 and 50% of MM patients, respectively [3]. Moreover, the development of CKD in MM patients is associated with a poor prognosis. Decourt *et al.* [4] reported a median survival of only 18.3 months in MM patients developing end-stage renal disease (ESRD). Because of this short survival, kidney transplantation was not considered a viable treatment option for patients with MM and ESRD until recently. This is changing with the improvement of long-term survival in MM patients because of the introduction of new therapeutic agents for MM patients with CKD.

There is limited but growing evidence that certain MM patients can successfully undergo renal transplantation after ASCT. The number of MM patients that have received a kidney transplant is low, and different strategies have been applied. In the past, kidney transplantation was only considered for MM patients years after they attained complete remission following induction therapy (in that era, most often using dexamethasone and melphalan). However, MM relapse and death from

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infectious complications are frequent using this treatment approach [5–12]. A small group of patients received Autologous Stem Cell Transplant (ASCT) and a kidney transplant from the same donor. This approach can be successful but has a limited application as a suitable living donor is a prerequisite [13, 14]. More recently, several groups have reported on the outcome of kidney transplantation in MM patients treated with chemotherapy and ASCT [15–21]. Until now, only 18 MM patients treated with SCT followed by kidney transplantation have been reported in the literature to the best of our knowledge. Some patients achieved long-term survival without MM relapse and good allograft survival; however, MM relapse, cardiovascular and infectious complications, allograft failure due to rejection and patient death appear to be common in this patient population. The article of Shah *et al.* [22] in this issue of *Clinical Kidney Journal* further adds to the literature and highlights the challenges faced in MM patients undergoing kidney transplantation [22].

In their article, Shah *et al.* [22] report five MM patients with ESRD undergoing kidney transplantation. These patients attained a very good partial remission or complete remission following induction therapy using novel agents, and subsequently underwent high-dose ASCT. Kidney transplantation was performed at a median of 27 months after ASCT. Post-transplant immunosuppressive treatment consisted of induction with basiliximab followed by maintenance therapy with tacrolimus, mycophenolate mofetil and prednisolone [22]. Two out of five patients experienced a relapse of MM at 6 and 16 months after kidney transplantation and both patients died (at a median of 52 months post-transplant). The other three patients do not have evidence of MM relapse. However, two of these patients experienced allograft rejection and returned to dialysis at a median of 39 months post-transplantation. The three patients without MM relapse are alive at a median time of 55 months post-transplantation resulting in a death-censored graft and patient survival of 80% at 4 years post-transplantation [22].

There are several outstanding questions regarding selection and optimal management of MM patients for kidney transplantation. Early relapse in MM can often be predicted by the presence of adverse myeloma genetics or high proliferative index [23]. These results are not provided in the published article, but have potential use in the selection processes in eliminating patients likely to progress within 24 months following their first remission. The issue of early relapse relates to the biggest challenge: the identification of MM patients most suitable to receive a renal allograft considering the scarcity of renal allografts. This selection should ensure that MM patients' survival is expected to be prolonged post-kidney transplantation. Several stratification systems exist combining genetic information, fluorescence *in situ* hybridization or gene profile expressing. However, estimating a patient's risk of MM relapse/progression according to the current stratification systems seems to be imperfect to identify individuals with a greater likelihood of long-term survivorship and graft longevity. Novel risk stratification systems are warranted for better selection of MM patients suitable for renal transplantation and, in our opinion, minimal residual disease (MRD) status should be incorporated into these risk stratification systems [24]. Without a doubt, standard risk MM patients with persistent MRD-negative status would be excellent candidates to undergo renal transplantation. However, it remains to be established if sustained MRD-negative status is an absolute prerequisite for successful renal transplantation in order to prevent exclusion of candidates who could benefit from renal transplantation even with MRD being present at the time of renal transplantation [2]. Despite current treatment options, patients with high-risk MM who do not achieve MRD-negative status do not enjoy long-term survival and have a greater risk of early relapse and disease progression and, thus, should not be offered a kidney transplant. In contrast, high-risk MM patients achieving sustained MRD-negative status have improved outcomes and should be considered for renal transplantation [25]. Immunomodulatory drug-based maintenance therapy following ASCT has greatly improved outcomes. However, several case reports have shown lenalidomide to be associated with the occurrence of, often treatment-resistant, solid organ allograft rejection, in MM patients [26, 27]. In addition, a recent report showed that initiation of pomalidomide was complicated by the development of acute kidney injury necessitating allograft nephrectomy with histologic evidence of severe acute rejection [28]. Currently, the exact place of immunomodulatory drugs in maintenance treatment or as treatment of MM relapse in renal transplant recipients is unclear and needs to be carefully established. It might be an option to use other drugs such as bortezomib, ixazomib and daratumumab, especially early after renal transplantation. Another strategy would be to omit maintenance therapy in low-risk MM patients with persistent MRD-negative status following ASCT.

The next question concerns the optimal waiting time before renal transplantation for MM patients: how long should the relapse-free period be before renal transplantation is beneficial for both patient and society? Too long a period would deny patients who could potentially benefit from earlier renal transplantation. Too short a period would result in suboptimal patient and allograft outcomes post-transplantation. A potential approach could be, a minimum 6-month waiting period in patients with low-risk MM, a minimum 12-month waiting period in MM patients with standard risk and in MM patients with high risk, with sustained MRD-negative status. Patients with high risk not achieving sustained MRD-negative status should not be offered renal transplantation at this time.

Finally, infections are a common cause of death in MM patients with ESRD [4]. However, in the published cases of MM patients undergoing kidney transplantation, there does not seem to be an excess of post-transplant infections. It is not clear whether this is due to a true absence of excess of infections, lack of granularity of the available data or possible publication bias in favour of patients with positive outcomes.

In conclusion, based on the limited available data, renal transplantation might be a viable treatment option for MM patients with ESRD and these patients will be increasingly referred for evaluation for kidney transplantation. MM patients with ESRD considered for renal transplantation should ideally be treated with anti-myeloma induction therapy followed by ASCT and maintenance therapy in standard- and high-risk patients. It is important to note ASCT-associated toxicity in patients with advanced CKD even despite the use of reduced dose conditioning [29]. Strategies need to be developed to prevent this added burden to improve post-transplant outcomes. The optimal immunosuppressive and MM treatment post-transplant remains to be established and, therefore, multicentre data- and experience-sharing should be encouraged in order to accelerate progress in this field.

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CONFLICT OF INTEREST STATEMENT

None declared.

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