Defining the Role of Renal Transplantation in the Modern Management of Multiple Myeloma and Other Plasma Cell Dyscrasias

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\textbf{Abstract}

Plasma cell dyscrasias (PCD) are due to an abnormal proliferation of a single clone of plasma or lymphoplasmacytic cells leading to secretion of immunoglobulin (Ig) or an Ig fragment, causing the dysfunction of multiple organs. Median survival of these patients has significantly improved over the last decade due to availability of treatment options such as high-dose melphalan with autologous stem cell transplantation and novel anti-myeloma agents. Renal transplantation has not traditionally been considered in these patients due to the previously limited prognosis, along with concerns relating to disease recurrence affecting the renal allograft and increased infection susceptibility following renal transplant due to immunosuppression and the PCD itself. However, with the increasing range of effective treatment options, renal transplantation could now be considered, especially in young patients with good performance status. It is therefore timely to reappraise the potential role of renal transplantation in end-stage renal disease due to multiple myeloma and other PCD. This review summarizes the literature relating to renal transplantation in PCD, including multiple myeloma, monoclonal Ig deposition disease and systemic AL amyloidosis, to attempt to identify patients who may benefit most from this approach and to explore areas for further development.

\textbf{Key Words}

Plasma cell dyscrasias · Multiple myeloma · Monoclonal immunoglobulin deposition disease · Light chain deposition disease · Renal transplantation · Amyloidosis · Autologous stem cell transplantation

\textbf{Introduction}

Plasma cell dyscrasias (PCD) represent a spectrum of diseases characterized by abnormal proliferation of a single clone of plasma cells or lymphoplasmacytic cells. Under normal circumstances these cells secrete functional immunoglobulin (Ig) necessary for humoral immunity. In the transformed state, abnormal production and secretion of monoclonal Ig (M Ig) or fragments occur and its deposition in various tissues causes organ dysfunction. PCD include the premalignant monoclonal gammopathy of unknown significance (MGUS), solitary plasmacytoma, Ig-mediated amyloidosis (AL amyloidosis), and both asymptomatic and symptomatic multiple myeloma (MM) (fig. 1).
MM is a PCD that accounts for almost 10% of all hematological malignancies [1]. The annual incidence of MM in the UK is 60–70 per million [2]. The overall prevalence is likely to be increasing given the recently published data demonstrating improved survival rates over the last decade [3].

Renal Manifestations of PCD

Renal impairment is a common and potentially serious complication of PCD occurring at presentation in 20–25% patients and in up to 50% of patients at some time during their disease [4]. Approximately half of the patients recover on supportive treatment and 2–12% of the rest progress to end-stage renal disease (ESRD) requiring renal replacement therapy [5].

The three most common renal manifestations of PCD are: (1) MM with cast nephropathy caused by glomerular filtration and deposition of Ig light chains leading to distal tubule obstruction and associated tubulointerstitial nephritis. The typical clinical presentation is with acute kidney injury, often in the context of intercurrent infection or dehydration, and is frequently a presenting feature of MM. (2) Monoclonal immunoglobulin deposition disease (MIDD) due to deposition of intact or fragments of light chains (light chain deposition disease or LCDD) and/or heavy chains along glomerular and/or tubular basement membrane. Patients with MIDD typically have nephrotic range proteinuria and progressive chronic kidney disease. (3) AL amyloidosis in which β-pleated sheets are formed by light chains or light chain fragments and is deposited in glomeruli and other renal blood vessels. Again, nephrotic syndrome with progressive chronic kidney disease is a typical mode of presentation. AL amyloidosis is a systemic disease and so non-renal features including neuropathy, cardiomyopathy and gastrointestinal disease are often present.

In a native renal biopsy study in patients with MM, cast nephropathy was found in 40–63% of patients, LCDD in 19–26%, and AL amyloidosis in 7–30% of patients [6]. The latter two lesions may or may not be associated with clinical evidence to fulfil the diagnostic criteria of MM (fig. 1). There is significant overlap in their presentation such that cast formation may also be seen in up to a third of cases of LCDD but rare in AL amyloidosis.

Risk Stratification and Outcomes in PCD with Renal Dysfunction

The presence of renal disease in patients with MM is of prognostic importance because it is associated with a significant increase in morbidity and mortality [7]. In United Kingdom Medical Research Council MM trials between 1980 and 2002, 10% early mortality (within 60 days of diagnosis) was reported of which renal failure contributed to 28% [8]. Median survival on dialysis of 6, 48 and 22 months in cast nephropathy, MIDD and amyloidosis, respectively, has been reported [6]. Median survival in patients presenting with cast nephropathy with serum creatinine of <125, 125–175 and >175 μmol/l was reported as 44, 18 and 4 months, respectively. These data predate more frequent use of novel agents and stem cell transplantation (SCT) [9].

Significant renal dysfunction at the time of presentation and poor response to chemotherapy has been implicated as a marker of poor prognosis [7]. Recently, multiple studies have reported significantly improved survival in patients with MM over the last decade. The improvement

Fig. 1. Venn diagram representing relationship between different renal pathologies in PCD. Patients with PCD may present with renal disease due to cast nephropathy, MIDD or AL amyloid. Patients with cast nephropathy all fulfill diagnostic criteria for MM but this is not the case in MIDD and AL amyloid. MGUS may evolve into MM with or without cast nephropathy but may also present with AL amyloid or MIDD in the absence of MM (arrows). Thus, although MGUS is conventionally considered to be a benign condition, it may still result in serious renal pathology. Note that renal lesions may coexist.
in survival was seen predominantly among patients younger than age 65 years at diagnosis, with a median overall survival of 56.3–60 months [10–12].

Treatment of PCD in Renal Dysfunction

The main aims of treatment in PCD are to control disease, maximize quality of life and prolong survival. The initial goal is to induce a remission in the underlying malignancy with chemotherapy regimens. Suitable patients are then considered for high-dose melphalan (HDM) followed by autologous stem cell transplantation (ASCT) that remains the standard of care. After more than 20 years’ experience of HDM/ASCT and with the use of dose-reduced conditioning regimens, it is now recognized as a feasible treatment modality in patients with renal failure, including those requiring dialysis. It has been shown to improve outcome in patients with renal dysfunction, more likely if started early [6, 11].

The introduction of novel agents such as thalidomide, lenalidomide and bortezomib (usually in combination with dexamethasone) has also led to major improvements in survival of patients with MM [12]. These agents may be used in patients with renal dysfunction and, if administered at an early stage, may be successful in reversing and preventing permanent renal damage [13, 14].

In patients presenting with renal dysfunction, renal recovery is improved with early reduction in serum monoclonal free light chains (FLC) [15–17]. In a recent study, Hutchison et al. [18] concluded that a FLC reduction of 60% by day 21 could lead to 80% of patients recovering sufficient renal function. In their study the median survival was 42.7 months (range 0–80) among those who recovered function compared with 7.8 months (range 0–21) among those who did not (p < 0.02).

FLC removal by extended haemodialysis employing a high cut-off dialyser is under evaluation as a novel therapeutic option. In an ongoing European trial, participants are randomized to either FLC removal by high cut-off extended haemodialysis or standard high-flux haemodialysis. Each group will receive the trial chemotherapy regimen of bortezomib, doxorubicin and dexamethasone [19].

Small numbers of patients with MM and ESRD have successfully been treated with non-myeloablative conditioning followed by simultaneous renal and allogeneic SCT from an HLA-identical sibling. In some cases this has achieved complete remission of myeloma as well as stable renal allograft function without a requirement for immunosuppression; engrafted donor immune cells facilitate functional immunological tolerance of the renal allograft [20]. This novel treatment is now being investigated in a clinical trial [21].

A detailed discussion of the treatment of MIDD and AL amyloidosis is beyond the scope of this review, but in general terms the range of therapies is similar to that used in MM.

Renal Transplant in PCD

Renal transplantation for patients with PCD is rarely considered given the nature of the disease and risk of post-transplant infections and disease recurrence. It has been suggested that renal allograft outcomes are determined both by the remission status of the PCD and by the inherent toxicity of the MIg [22]. With the improvement in overall survival in PCD, a carefully selected group of patients may benefit from renal transplant and should be considered if they are in durable remission for 3–5 years.

Multiple Myeloma with Cast Nephropathy

There are a number of isolated reports describing renal transplantation in patients with cast nephropathy coming from specialized centres. In one early series, survival ranging from 14 to 114 months was reported in 9 MM patients who had renal transplantation [23]. In this study, one third of patients died of progressive myeloma and a third from sepsis. No disease-related graft loss was reported in spite of recurrence in some cases. All patients reported improved quality of life and remained off dialysis post-transplantation. Similar outcomes have been reported in subsequent studies (table 1). These series suggest that cast nephropathy does not routinely recur in allograft if MM is in remission at the time of transplantation. In a European registry study, 1.4% of MM patients had renal transplantation during renal replacement therapy follow-up. One third of these patients received living donor transplantation and their median survival was 9.6 years [27]. As no data regarding patient selection was available, it is possible that improved outcome could also be due to selection of healthier patients for transplant and reporting bias.

As mentioned earlier, attempts have been made to achieve specific tolerance and potent anti-myeloma response by combined renal and SCT. In a recent update, Spitzer et al. [28] reported the outcome in 7 patients with
MM and ESRD who underwent a combined HLA-matched renal and SCT. Patients received high-dose cyclophosphamide, equine anti-thymocyte globulin and thymic irradiation pre-transplant and cyclosporin as sole post-transplant immunosuppression, which was tapered and discontinued as early as day 73 post-transplant. One patient died of MM recurrence and progression in spite of multiple salvage treatments, and another of acute myeloid leukaemia after developing a therapy-related myelodysplastic syndrome. Two patients had to be re-started on immunosuppression due to graft-versus-host disease. Three patients have normal or near normal renal function without any immunosuppression. This study suggests that it is possible to achieve sustained renal allograft tolerance and prolonged anti-myeloma response by combined HLA-matched renal and SCT. However, the technique is highly specialized and remains an area for clinical research rather than routine clinical practice. Even if the results improve as the technique is refined, it is likely to be restricted to highly specialized centres with the necessary resources and expertise.

European Best Practice Guidelines advise a waiting period of at least 2 years between successful induction treatment and renal transplantation [29]. However, with the availability of newer and more potent drugs, ASCT and novel treatment regimens, it is reasonable to re-appraise these recommendations. As recurrence of cast nephropathy in the renal allograft appears low in patients who remain in remission for 3–5 years, it is argued that a special case should be made for these patients in an era where repeated periods of disease control and prolonged survival may be achievable with modern MM treatments. The recommended delay of 2 years may not be logical in this population where progression is ultimately expected, and a more appropriate time for renal transplantation would be shortly after induction of first remission and consolidation with ASCT. Furthermore, restoring GFR may increase the range and intensity of anti-myeloma treatments, and thereby improve long-term survival. Clearly, such patients need to be carefully selected, based on patient age and overall prognosis of MM, as well as patient preference following comprehensive counselling. In our opinion, a waiting period of 2–5 years may not be appropriate in a small number of selected patients who could have high dialysis-associated morbidity and mortality.

### Table 1. Outcome of renal transplantation in MM-cast nephropathy

<table>
<thead>
<tr>
<th>Study type</th>
<th>Patient outcome</th>
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<tbody>
<tr>
<td>De Lima et al. [24]</td>
<td>Case report</td>
</tr>
<tr>
<td>Walker and Bear [25]</td>
<td>Case report</td>
</tr>
<tr>
<td>Van Bommel [23]</td>
<td>Review</td>
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<tr>
<td>Dagher et al. [26]</td>
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### Monoclonal Immunoglobulin Deposition Disease

Renal transplantation is generally not considered in patients with MIDD due to almost universal recurrence of the disease and poor survival of the allograft, though a small number of transplants have been performed with the possibility of prolonging patient survival. Early recurrence in the allograft is more common in MIDD patients in whom necrotizing or crescentic glomerulonephritis or membranoproliferative glomerulonephritis is a primary presentation of PCD in native kidneys [30]. Presence of both light and heavy chains by immunofixation also appears to be risk factor for early recurrence. Earlier case reports and series showed a poor outcome and high recurrence rate in the renal allograft with the use of conventional chemotherapy [31]. In a study published by Leung et al. [31], 7 patients with LCDD received a renal transplant. Only 3 patients had received chemotherapy with melphalan and prednisolone prior to renal transplant, while 4 of them received other regimens. LCDD recurred in 5 patients after a median of 33.3 months and 4 of them died. Only 1 patient remained recurrence-free. Median allograft survival rate was only 37.3 months in patients with LCDD.

Role of Renal Transplantation in the Management of MM and Other PCD

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c231
More recently, myeloablative therapy with HDM and ASCT were shown to achieve more sustained responses in these patients (table 2). This therapy has been shown to be safe and effective treatment for MIDD. Haematological remission (HR) could be achieved in up to 90% of patients with 60% achieving complete remission (CR). Though 67% have been shown to relapse after a median of 3 years, these patients could then be considered either for further treatments, including novel agents. Current European guidelines consider LCDD as a contraindication for renal transplantation [29]. This recommendation needs to be reviewed in light of recent advances in treatment of patients with MIDD. At present there is very limited experience of renal transplantation in patients with MIDD who have received HDM/ASCT. In the case series mentioned above, outcomes following renal transplantation have been generally good. However, owing to its infrequent use, multicentre studies and registry-based data are needed to establish the optimal sequence of treatments for patients with MIDD.

**AL Amyloidosis**

Early experiences with renal transplantation in amyloidosis showed poor outcome with high post-transplant mortality and graft loss [36]. The majority of these patients had secondary amyloidosis due to inflammatory conditions. Hartmann et al. [37] published their 15-year experience of renal transplantation in patients with AL amyloidosis and showed a 5-year graft survival of 65%, although 74% of these patients had secondary amyloidosis due to rheumatic disease. No difference in outcome between primary and secondary disease was observed. Leung et al. [38] reported the outcome in 8 patients with AL amyloidosis who underwent living donor renal transplantation receiving standard induction and maintenance transplant immunosuppression. Five patients subsequently had ASCT. They reported 2 deaths due to post-transplant complications. Two patients had a subclinical and 1 a clinical acute cellular rejection easily treated with corticosteroids. The authors highlighted the feasibility of sequential living donor renal transplant and ASCT for carefully selected patients. Table 3 summarizes the outcome of renal transplantation in patients with AL amyloidosis in two of the biggest series so far. These studies have shown a renal allograft survival ranging from 18 to 72 months without clinical or histological evidence of recurrence. These data suggest that renal transplantation could be considered in patients with preserved performance status, who have little or no clinically significant amyloid deposition in other organs and have at least achieved a partial remission with chemotherapy with or without ASCT. Currently there is no evidence that intensive approach has any additional benefit as compare to conventional treatment. Though there is no clear guidance regarding renal transplantation in AL amyloidosis in current European Best Practice Guidelines, it has not been considered as an absolute contraindication [29]. These patients should have a careful work-up including extensive cardiac assessment before they are considered for transplantation.

<table>
<thead>
<tr>
<th>Table 2. Outcome of sequential ASCT and renal transplantation in MIDD</th>
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<tr>
<td>Patients receiving kidney transplant, n</td>
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<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Royer et al. [32] 1</td>
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<tr>
<td>Hassoun et al. [33] 2</td>
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<tr>
<td>Lorenz et al. [34] 1</td>
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<td>Girnius et al. [35] 2</td>
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<td>Bansal et al. [36] 1</td>
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CR = Complete remission.
Conclusion

The mainstay of management of renal failure in MM and other PCD has to centre on prevention, stabilization and, where possible, reversal. However, there will inevitably be occasional patients where irreversible, end-stage renal failure will be a complication early in the course of the PCD. Ongoing renal support in these patients enables administration of chemotherapy and novel agents sufficient to result in prolonged periods of disease suppression, but long-term dialysis will ultimately lead to compromised clinical outcome and quality of life.

The suitability of any patient for renal transplantation is determined by an assessment of the balance of risk versus the likely benefit. Benefits include those related to quality of life as well as survival advantage over dialysis. Predicting survival advantage for an individual patient can be very difficult in practice, but for patients with PCD it has generally been judged that transplantation is unlikely to be of benefit. Disease recurrence affecting the renal allograft, increased infection susceptibility and poor prognosis have been major concerns in these patients, limiting this treatment to anecdotal reports of highly selected cases. However, major improvements in the overall and progression-free survival due to newer treatment options, lead us to challenge the perception that patients with PCD are never suitable candidates for renal transplantation. As sustained periods of disease stabilization are currently possible, we suggest that renal transplantation may now be considered early in the course of the disease, especially in dialysis-dependent younger patients with a good performance status. In such patients, waiting for 3–5 years of sustained disease control to elapse appropriate before renal transplantation is not appropriate if the benefits of renal transplantation are to be maximized. It is acknowledged that many of the patients with MM on dialysis are elderly, frail, have a limited life expectancy despite treatment advances and will remain unsuitable candidates for HDM/ASCT and renal transplantation.

Due to rarity of these patients, prospective clinical trials will be challenging and, in the first instance, data registry reporting of MM or PCD patients treated with renal transplantation is warranted. Such patients can then be tracked to assess various aspects, such as post-transplant infection rates, health-related quality of life, and how recurrence of MM and PCD with re-institution of treatment affects renal and overall outcomes.

It is important that donor and recipient are made aware of the risk of early graft loss due to recurrence of disease. Immunological risk will be a factor in determining the safety of this approach as low-risk patients can be managed with minimization of immunosuppression to reduce the burden of infectious complications in a population that already has a significant immune deficit because of previous therapies to treat the PCD.

Until further expertise is gained and the role of renal transplant is better defined, the main emphasis in managing these conditions would be on rapid removal of FLC with aggressive chemotherapeutic agents with or without physical removal by using specialized renal replacement techniques. These patients should further be considered for renal transplant if they progress to ESRD and if sustained remission can be achieved.

Acknowledgement

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References

21. Combined bone marrow transplantation (BMT) and renal transplant for multiple myeloma (MM) with end-stage renal disease (ESRD) NCT00854139 Clinical Trials.gov.
Bansal et al. elegantly review the impact of plasma cell dyscrasias (PCD) on the kidney. They make a very informative contribution when they put the prognosis of a range of PCD into the context of current advances in therapy. This opens the door to a review of current attitudes relating to renal transplantation of patients suffering from these conditions – multiple myeloma, monoclonal immunoglobulin deposition disease as well as AL amyloidosis.

Nephrologists are occasionally faced with decisions related to renal replacement therapy in patients with malignancies including PCD. An important decision-making factor to consider is the extent of comorbidities affecting these patients. Comorbidities have been shown to affect progression-free survival and overall survival in multiple myeloma patients. Beside the severity of CKD and age, impaired lung function and a poor Karnofsky performance status were significant predictors of overall survival. A combination of these risk factors within the Freiburger comorbidity index identifies significantly different median survival rates of 118, 53 and 25 months with 0, 1 and 2 or 3 risk factors, respectively [1]. In light of these observations, comorbidities are critical prognostic determinants of morbidity and mortality in patients with PCD and warrant careful consideration when renal replacement therapy and renal transplantation are considered in such patients. Solid organ transplantation (heart and kidney) should be considered in PCD patients as prolonged graft and patient survival may be obtained, providing that recipients do not have other severe comorbidities and that haematological remission has been achieved with chemotherapy before or after organ transplantation [2]. Finally, decision-making should be multidisciplinary with involvement of nephrologists and haematologists. And don’t forget to involve the patient...!

References
