Long-term outcome of autologous stem cell transplantation in light chain deposition disease

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Abstract

Background. Light chain deposition disease (LCDD) is a systemic disorder characterized by deposition of non-amyloid monoclonal light chains. Renal dysfunction is a ubiquitous manifestation of the LCDD disease. Reports suggest that high-dose chemotherapy and autologous stem cell transplantation (ASCT) may be beneficial in the treatment of LCDD. However, the impact of ASCT on renal function is unclear. This study retrospectively reviewed the effect of ASCT on renal function in patients with LCDD.

Methods. Six patients with LCDD have been transplanted at our institution since 2001. Patients received dexamethasone alone, dexamethasone plus thalidomide or no chemotherapy prior to conditioning. All the patients underwent high-dose melphalan conditioning after stem cell mobilization.

Results. Three of the six patients had concurrent multiple myeloma (MM), and one patient was on haemodialysis prior to transplantation. Four patients were male and two were female. The median age was 43.5 years with a median serum creatinine of 2.4 mg/dl and a median estimated glomerular filtration rate (eGFR) of 26.5 ml/min/1.73 m². Five patients survived ASCT and one died on Day 26 of transplantation. Median follow-up was 31.7 months (range 31.3–60.7 months) after ASCT. Of the surviving patients, all the five achieved a haematological response post-transplantation although two ultimately relapsed and required further chemotherapy. The eGFR of one patient declined with relapse and improved with treatment, while the eGFR of the second patient remained stable throughout relapse and treatment. The patient on haemodialysis prior to transplantation continued to require it afterward, but ultimately received a renal transplant. Median reduction in proteinuria was 92% and median improvement in eGFR was 95%. Of the four evaluable patients all achieved criteria for a renal response after ASCT.

Conclusions. ASCT may be an effective therapy for renal dysfunction associated with LCDD. In cases where kidney dysfunction persists after ASCT, a haematological response may permit successful kidney transplantation with improved graft viability and decreased risk of recurrence.

Keywords: light chain deposition disease; monoclonal gammopathy; paraproteinemia; renal dysfunction; stem cell transplantation

Introduction

Light chain deposition disease (LCDD) is a systemic disorder characterized by deposition of monoclonal light chains in various organs. A single clone of plasma cells is responsible for the overproduction of either kappa or rarely lambda light chains [1]. Even in the absence of detectable serum or urine monoclonal immunoglobulin, a monoclonal population of bone marrow plasma cells can be demonstrated via immunofluorescence [2]. While many cases of LCDD are associated with multiple myeloma (MM), up to 50% of patients do not have concurrent MM [3].

Light chain deposition can occur in any organ [4]. Renal dysfunction generally dominates the clinical picture due to progressive accumulation of light chains from plasma filtration [5]. Kidney dysfunction is manifested by proteinuria, nephrotic syndrome and renal insufficiency [4]. If left untreated, most of the patients with LCDD will develop end-stage renal disease [3]. The next most common organ to be involved is the heart; cardiac symptoms include arrhythmias and congestive heart failure [4]. Liver involvement may be asymptomatic or manifest with mild transaminase elevation, portal hypertension or fulminant liver failure [4]. Pulmonary involvement has also been reported. Pulmonary cystic disorder is a rare but serious complication of LCDD that may cause respiratory insufficiency requiring lung transplantation [6].

LCDD is defined by several characteristic histologic features on renal biopsy. On light microscopy, nodular glomerulosclerosis resembling Kimmelstiel–Wilson lesions is characteristic but is neither pathognomonic nor universal [4]. Immunofluorescence is the most sensitive
method used to diagnose LCDD. Nearly all renal biopsies show linear deposits of monoclonal light chain along a tubular basement membrane [4]. These deposits are also evident on electron microscopy as unorganized deposits in a granular fashion [7]. Unlike amyloidogenic light chains, light chains in LCDD do not form fibrils and do not show birefringence with Congo red stain [7]. Glomerular deposits may be seen with electron microscopy but not with immunofluorescence, possibly due to modifications of the light chains after deposition [8].

No standard treatment has been established for LCDD. Steroids plus melphalan or a cytotoxic agent have been used for LCDD with and without MM [4]. While some studies suggest that chemotherapy may slow renal decline [9,10], response is generally limited [3]. Kidney transplantation by itself has limited benefits since the disease tends to recur after transplantation [7]. Autologous stem cell transplantation (ASCT) has recently been reported to cause significant, sustained improvement in renal function due to LCDD [11–13]. We performed a retrospective study of the effect of ASCT on renal function in patients with LCDD at our institution.

Subjects and methods

The Mayo Dysproteinemia Database was queried for all patients with LCDD who had undergone ASCT. Patients with coexistent MM were included in this study. However, in none of the patients was proteinuria or creatinine elevation due to cast nephropathy. Diagnostic criteria for MM have been published previously [14]. Patients with amyloidosis were excluded. All patients gave written informed consent prior to study entry. The protocol and consent form were approved by the Institutional Review Board of the Mayo Foundation in accordance with the Declaration of Helsinki. Relevant information regarding ASCT, treatment and follow-up were extracted from patients’ records at Mayo Clinic.

LCDD was diagnosed by renal biopsy. All the renal biopsies were processed for light microscopy and immunofluorescence according to standard techniques. Electron microscopy was performed on five of the six native biopsies. LCDD was defined by the presence of characteristic linear monoclonal light-chain deposits along the tubular basement membrane staining for kappa or lambda chains on immunofluorescence. Patients with coexistent cast nephropathy were excluded.

All patients underwent baseline evaluation of their LCDD. Monoclonal immunoglobulin in serum and urine was identified by electrophoresis and immunofixation. Serum free light chain was measured in five patients but the assay was not available at the time of diagnosis of one patient. Echocardiography was used to assess possible cardiac involvement. The eGFR was predicted by the Modification of Diet in Renal Disease (MDRD) Study equation [15]. Baseline albumin levels were assessed. Bone marrow biopsies were performed in all the patients.

Treatment prior to high-dose therapy and ASCT was recorded. Prior to transplantation, patients received either no chemotherapy, dexamethasone alone or dexamethasone plus thalidomide. Dexamethasone was administered at 40 mg/day on Days 1–4, 9–12 and 17–20 for variable treatment cycles. Thalidomide was administered at 200 mg/day. Stem cell mobilization was accomplished with sargramostim (GM-CSF) or filgrastim (G-CSF) (5 µg/kg/day). Apheresis was performed until a minimum of 2 × 10⁸/kg of CD34⁺ cells were collected. All patients underwent conditioning with high-dose melphalan. Engraftment was defined as the amount of time required to achieve 500/µl leukocytes and 50 000/µl platelets for 3 consecutive days.

Haematological and renal responses to therapy were assessed by criteria published previously [16]. Haematological response was defined as a decrease in serum free light chains or monoclonal protein of >50% or complete eradication of the monoclonal protein if it was too small to be quantified. Renal response was characterized by a 50% decrease in 24-h urine protein concentration with <25% decline in renal function.

Results

Between 13 September 2001 and 16 September 2004, six patients underwent stem cell transplantation. No patients were lost to follow-up. Pre-transplant characteristics are given in Table 1. All patients were Caucasian. The median age was 43.5 years (range 33–61 years). Four (67%) patients were male and two (33%) were female. Coexistent MM was diagnosed in three patients with plasma cells constituting 10%, 20% and 40% of the marrow in those patients. Two of the patients with MM were at Durie–Salmon Stage 2b and did not have myeloma bone disease. The third patient was at Stage 3b and did have myeloma bone disease. The remaining three patients did not have associated MM. One of the patients with LCDD not associated with MM had normal plasma cells on bone marrow biopsy constituting 1% of the marrow; the other two patients had monoclonal populations of plasma cells constituting 5% and 10–15% of the marrow. Three renal biopsies were performed at Mayo Clinic, while two biopsies were performed elsewhere and the pathology was reviewed at Mayo Clinic. One renal biopsy was performed elsewhere and not reviewed at Mayo Clinic.

Serum monoclonal (M) protein was not quantifiable in any of the patients prior to transplantation. Serum free light chain was quantifiable in five patients. Four patients had elevated levels of kappa free light chain with a median level of 11.44 mg/dl (normal range 0.33–1.94 mg/dl) and a median kappa/lambda ratio of 9.91 (normal range 0.26–1.65). One patient had an elevated level of lambda free light chain. His lambda free light chain level was 312 mg/dl after plasmapheresis (normal range 0.57–2.63 mg/dl) with a kappa/lambda ratio of <0.01 (normal range 0.26–1.65). A urine M-protein was detectable in two patients with a median value of 415 mg/day (range 47–783). Three bone marrow biopsies were performed at the Mayo Clinic. The remaining three were performed at outside institutions and the pathology was reviewed at the Mayo Clinic. Five biopsies demonstrated a population of monoclonal kappa plasma cells and one demonstrated a population of monoclonal lambda plasma cells. Median creatinine was 2.4 mg/dl and median creatinine clearance predicted by the
Table 1. Clinical characteristics of LCDD patients prior to autologous stem cell transplantation (ASCT)

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<tr>
<td>Age</td>
<td>56</td>
<td>61</td>
<td>44</td>
<td>43</td>
<td>39</td>
<td>33</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Concurrent multiple myeloma</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Type of light chain</td>
<td>Lambda</td>
<td>Kappa</td>
<td>Kappa</td>
<td>Kappa</td>
<td>Kappa</td>
<td>Kappa</td>
</tr>
<tr>
<td>sFLC at time of transplant (mg/dl)</td>
<td>312</td>
<td>19.6</td>
<td>2.18</td>
<td>N/A</td>
<td>3.28</td>
<td>45.3</td>
</tr>
<tr>
<td>Serum M-protein (g/dl)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Urine M-protein (mg/day)</td>
<td>783</td>
<td>47</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bone marrow % plasma cells</td>
<td>40% monoclonal</td>
<td>20% monoclonal</td>
<td>10% monoclonal</td>
<td>5% monoclonal</td>
<td>1% normal plasma cells</td>
<td>10–15% monoclonal</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.9</td>
<td>3.8</td>
<td>4.2</td>
<td>1.8</td>
<td>4.1</td>
<td>3.6</td>
</tr>
<tr>
<td>Hypertension</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Creatinine at presentation (mg/dl)</td>
<td>900</td>
<td>131</td>
<td>482</td>
<td>10 251</td>
<td>876</td>
<td>311</td>
</tr>
<tr>
<td>eGFR by MDRD at time of ASCT (ml/min/1.73 m²)</td>
<td>30</td>
<td>20</td>
<td>50</td>
<td>31</td>
<td>12</td>
<td>23</td>
</tr>
<tr>
<td>Proteinuria at time of ASCT (mg/day)</td>
<td>2.4</td>
<td>3.4</td>
<td>1.6</td>
<td>1.9</td>
<td>5.8</td>
<td>2.5</td>
</tr>
<tr>
<td>Pre-transplant treatment</td>
<td>Dexamethasone (3 months)</td>
<td>Dexamethasone (3 months)</td>
<td>Dexamethasone and thalidomide (4 months)</td>
<td>Dexamethasone (3 months)</td>
<td>Dexamethasone (3 months)</td>
<td>None</td>
</tr>
<tr>
<td>Conditioning regimen (mg/m²)</td>
<td>Melphalan 70 on Days −1, −2</td>
<td>Melphalan 70 on Days −1, −2</td>
<td>Melphalan 70 on Days −1, −2</td>
<td>Melphalan 200 on Day −1</td>
<td>Melphalan 140 on Day −1</td>
<td>Melphalan 140 on Day −1</td>
</tr>
</tbody>
</table>

sFLC = serum free light chains; MDRD = Modification of Diet in Renal Disease Study.

Table 2. Clinical characteristics of LCDD patients after autologous stem cell transplantation (ASCT)

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months of follow-up post-transplant (months)</td>
<td>37.0</td>
<td>31.3</td>
<td>31.6</td>
<td>60.7</td>
<td>31.7</td>
<td>N/A (expired)</td>
</tr>
<tr>
<td>Lowest creatinine post-transplant (mg/dl)</td>
<td>1.4</td>
<td>1.7</td>
<td>1.2</td>
<td>1.0</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Highest eGFR by MDRD (ml/min/1.73 m²)</td>
<td>55</td>
<td>43</td>
<td>70</td>
<td>64</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Alive</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Lowest proteinuria after ASCT (mg/day)</td>
<td>38</td>
<td>91</td>
<td>63</td>
<td>173</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Did not develop hypertension</td>
<td>Persistent hypertension</td>
<td>Persistent hypertension</td>
<td>Did not develop hypertension</td>
<td>Developed hypertension which eventually resolved</td>
<td>N/A</td>
</tr>
<tr>
<td>Post-transplant treatments</td>
<td>Numerous treatments for relapse, most recently lenalidomide</td>
<td>Lenalidomide and melphalan</td>
<td>None</td>
<td>None</td>
<td>Kidney transplant</td>
<td>None</td>
</tr>
</tbody>
</table>

MDRD = Modification of Diet in Renal Disease Study.

MDRD equation was 26.5 ml/min/1.73 m². One patient was on haemodialysis prior to transplant. Another patient had cardiac and liver involvement by light chains demonstrated on biopsy of the respective organs. The median time from diagnosis to transplantation was 168 days (range 136–255).

Prior to transplantation, four patients received dexamethasone for 3 months, one patient received combination therapy with dexamethasone plus thalidomide for 4 months and one patient received no chemotherapy. All six patients successfully underwent stem cell collection without significant complications. The median number of CD34+ stem cells procured was 9.6 × 10⁶/kg over a median 2.5 leukaphereses. The median time from initiation of leukapheresis to transplant was 11 days. All of the patients received pre-transplant conditioning with melphalan. Only one of the patients had been exposed to oral melphalan prior to conditioning, and he had received only one dose. One patient received 200 mg/m² of melphalan on Day −1. The other five patients received reduced doses of melphalan due to renal insufficiency.

Outcome after stem cell transplantation

One patient suffered multi-system organ failure and died 26 days after ASCT but five patients remain alive. Their post-transplant characteristics are listed in Table 2. All surviving patients engrafted successfully. The median number of days until leukocyte engraftment was 12.5. Five patients had a platelet count of 50 000/µl by Day 55, and one patient was dismissed from the hospital on Day 14 with
spontaneously rising platelet counts. The median duration of hospitalization for complications related to transplantation was 9 days. Of the five evaluable patients, two (33%) had post-transplant bacteremia, both with coagulase-negative Staphylococcus. Other observed complications included mucositis (33%) and diarrhea (33%). Of the five evaluable patients, no treatment-related decline in renal function was observed. All five achieved a haematological response after ASCT although two ultimately relapsed and required further chemotherapy. The first patient relapsed 7 months after ASCT. His eGFR at time of relapse had declined from 55 ml/min/1.73 m$^2$ to 28 ml/min/1.73 m$^2$. He was treated with numerous chemotherapy regimens with recurrent episodes of relapse. His most recent eGFR had improved to 41 ml/min/1.73 m$^2$ while receiving lenalidomide. The second patient relapsed 28 months after ASCT. His eGFR remained stable at 41 ml/min/1.73 m$^2$ at the time of relapse. He was treated with lenalidomide and melphalan and his eGFR did not change. Currently all five of the six surviving patients (83%) remain alive. Median follow-up was 31.7 months (range 31.3–60.7 months) after ASCT.

In general, renal parameters improved after ASCT. The patient on haemodialysis prior to transplantation continued to require haemodialysis afterward. However, he underwent renal transplantation at an outside institution ~9 months after ASCT. Twenty-three months after renal transplantation, his creatinine clearance predicted by the MDRD equation was 47 ml/min/1.73 m$^2$. Haematological and renal parameters showed no evidence of recurrence with normal serum free light chain levels and negative serum and urine immunofixation with normal range proteinuria (91 mg/day). Renal biopsy of the allograft was not performed. In the remaining four patients, the median reduction in proteinuria was 92% (see Figure 1). The median improvement in eGFR was 95% (see Figure 2). Of the surviving patients not on dialysis prior to transplantation, all four achieved a renal response after ASCT. The two patients who were hypertensive prior to ASCT continued to have hypertension after ASCT. One patient who did not have hypertension prior to ASCT developed it after ASCT.

**Discussion**

LCDD is a rare plasma cell dyscrasia characterized by systemic deposition of light chains. Renal involvement is nearly universal and patients manifest renal insufficiency and proteinuria. Patient survival can range from 1 month to 10 years after onset of symptoms [4]. Features associated with worse prognosis include concurrent MM [5] and higher creatinine at presentation [4,5].

The use of high-dose chemotherapy with stem cell support has recently been reported in LCDD [11–13]. While intensive chemotherapy and ASCT has been shown to induce haematological response [12], their effect on renal function is less clear. Our study reviewed the impact of high-dose chemotherapy with ASCT on renal function in patients with LCDD with and without MM. Our results suggest that ASCT can be an effective therapy for light chain deposition disease. Four patients survived ASCT and did not require dialysis. In those four patients, high-dose chemotherapy and ASCT led to a median reduction in proteinuria of 92%. Median improvement in eGFR was 95%. All four evaluable patients ultimately achieved a renal response characterized...
by a 50% decrease in 24-h urine protein concentration with <25% decline in renal function.

Overall high-dose chemotherapy and ASCT led to the expected toxicities of bacteremia, diarrhea and mucositis. One patient died of multi-system organ failure after transplantation but had diffuse systemic involvement of LCDD at presentation. Her case suggests that patients with extrarenal manifestations of LCDD, namely cardiac involvement, may be at higher risk with ASCT.

The largest study of ASCT in monoclonal immunoglobulin deposition disease (MIDD) to date was performed by Royer and colleagues in 2004 [17]. This study included 11 patients with MIDD, 2 of whom had light and heavy chain deposition disease. All of the patients had renal involvement with four requiring dialysis prior to ASCT and three with nephrotic-range proteinuria. The majority of their patients had extrarenal symptoms with cardiac involvement in seven patients. Median follow-up was 51 months. No treatment-related deterioration of renal function was observed. Complete haematological remission was obtained in six cases with histologic regression of monoclonal immunoglobulin deposits demonstrated in heart, liver or skin. After ASCT, serum creatinine improved by 50% or more in four patients and the nephrotic syndrome resolved in all the three patients. Three of the original 11 patients developed recurrent disease. Two of the relapsing patients developed progressive renal insufficiency and one died. One patient underwent renal transplantation 3 years after ASCT. Renal biopsy post-transplantation revealed light chain deposition despite haematological remission.

Both our study and the study by Royer et al. suggest that high-dose chemotherapy and ASCT improve renal and haematological manifestations of LCDD without excessive morbidity or mortality. However, despite all of the published studies, the experience of ASCT in this disease remains small. In addition, we acknowledge the limitations in our study. The data were collected retrospectively and its small sample size precluded statistical analysis. Studies with longer follow-up will be needed to determine whether improvement in renal function is sustained more than several years after ASCT. More experience is also needed about kidney transplantation after ASCT to determine whether ASCT reduces recurrence rate. However, the encouraging results from our small study warrants further trials with larger sample size.

Conflict of interest statement. None declared.

References

Received for publication: 1.8.07
Accepted in revised form: 6.12.07