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ORIGINAL ARTICLE

High-dose melphalan and auto-SCT in patients with monoclonal Ig deposition disease

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The treatment of monoclonal Ig deposition disease (MIDD) is controversial and not standardized. We report our experience with high dose melphalan and auto-SCT (HDM/auto-SCT) in seven patients with MIDD associated with underlying Durie-Salmon stage IB multiple myeloma, including five with light chain deposition disease, one with light and heavy chain deposition disease and one with light chain crystal deposition disease. The median age of these patients was 50 years; six of them were male subjects. A monoclonal κ-light chain was detected by Serum Free Light Chain Assay in all seven. The patients received melphalan 140 mg/m^2 followed by auto-SCT. All patients are alive and six remain in hematologic CR with a median follow up of 23.6 months (7.9–69.8 months). Renal function has improved compared to pre-HDSM/auto-SCT in five patients—two of whom had a renal transplant and became dialysis independent—remained stable in one and worsened in one leading to hemodialysis despite hematologic CR. Our results corroborate previous experience with HDM/auto-SCT in MIDD and argue in favor of kidney transplantation in patients who achieve hematologic CR after HDM/auto-SCT. Although this approach appears effective, multi-center studies are needed to define the optimal treatment for patients with MIDD.
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Introduction

Monoclonal Ig deposition disease (MIDD) is a broad entity encompassing several conditions that result from the deposition of a monoclonal paraprotein in various organs.[1–3] It includes light chain deposition disease (LCDD), the most common pathology; light and heavy chain deposition disease (LHCDD) and heavy chain deposition disease. The latter two conditions are rare and have been poorly characterized in the literature. The major target organ in MIDD is the kidney, where the monoclonal paraprotein deposits within the glomerular basement membranes, mesangium, tubular basement membranes and vessel walls. This deposition typically leads to a nodular sclerosing glomerulopathy that eventually manifests with nephrotic syndrome, hypertension and renal insufficiency. Less commonly, other visceral organs can be involved, including heart and liver.[1,2,4–8] Also classified among MIDD is another entity known as light chain crystal deposition disease (LCCDD) described initially by Terashima.[9] LCCDD has received less attention because of its rarity and has been described in patients with lymphocytic and plasmacytic disorders. The pathology in this condition consists of light chain deposition forming intracellular crystals in histiocytes and renal parenchymal cells, particularly the proximal tubular epithelium, with variable involvement of other organs. Proximal tubular involvement typically manifests with light chain Fanconi syndrome, which is characterized clinically by type II renal tubular acidosis that associates a non-anion gap metabolic acidosis with hypophosphatemia, glucosuria and hypouricemia. Light microscopy reveals proximal tubular injury, although the intracytoplasmic crystals may be difficult to demonstrate without the aid of immunofluorescence and electron microscopy.

Monoclonal Ig deposition disease results from the production of a monoclonal paraprotein (light chain, heavy chain or both) and is, therefore, associated with an underlying plasma cell dyscrasia that may or may not be overtly diagnosed at the time patients first present with the disease. However, not all cases of MIDD have a demonstrable monoclonal protein by serum or urine protein electrophoresis and IF.[1,2,10] However, using the Free Light Chain Assay, which is more sensitive for the detection of serum free light chains, it is likely that virtually all patients with MIDD will have a monoclonal free light chain detected in the serum.

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The treatment of MIDD has not been standardized and remains controversial because of the small number of patients reported in the literature. However, as MIDD is associated with plasma cell dyscrasias, patients have typically been treated with regimens used for multiple myeloma, most commonly melphalan and prednisone and VAD (VCR, Adriamycin and Prednisone).[1,11,12] In a few small series, investigators have reported that high-dose melphalan (HDM) chemotherapy followed by auto-SCT can be associated with beneficial results whereas toxicity remains acceptable in this group of patients.[1,13–17] HDM/auto-SCT is a therapeutic modality currently accepted as the standard of care for patients with multiple myeloma who are less than 65 years of age. Here, we report our experience using HDM with auto-SCT in seven patients with MIDD, including four with LCCD, one with LHCDD and one with LCCDD. We show that this is a reasonable therapeutic option and that it can lead to effective control of the monoclonal free light chain production as well as stabilization and even improvement of renal function.

Materials and methods

Patient selection and evaluation

We retrospectively reviewed the records of all patients with MIDD who were treated with HDM/auto-SCT at Memorial Sloan Kettering Cancer Center between 2004 and 2007. We identified seven patients with monoclonal plasma cell dyscrasia and MIDD who underwent HDM/auto-SCT. Pretreatment evaluation included complete blood cell counts, renal and liver function tests, serum electrolytes, albumin, β2-microglobulin, C-reactive protein, calcium, HIV 1/2 test and β-HCG for women of childbearing potential. Monoclonal protein assessment included serum protein electrophoresis, immunofixation (IF), quantitative Igs and Free Light Chain Assay; 24 h urine for total protein determination, IF, protein electrophoresis, N-telopeptides and creatinine clearance. A skeletal survey was obtained prior to therapy. BM assessment included histologic examination of stained aspirate and biopsy specimen, flow cytometry analysis for κ/ λ clonal excess, CD138 and κ/ λ immunohistochemical staining and cytogenetic analysis with FISH for abnormalities of chromosomes 11, 13 and 14. All patients fulfilled the standard criteria for multiple myeloma based on the presence of plasmacytosis exceeding 10% of the nucleated BM cells and the presence a monoclonal gammopathy detected by serum or urine protein electrophoresis, IF or Serum Free Light Chain Assay. Patients were staged by the Durie–Salmon staging system and the International Staging System (ISS).[18]

To evaluate the etiology of the renal dysfunction, all patients underwent kidney biopsy and had the diagnosis of κ-light chain related MIDD confirmed by light microscopy, immunofluorescence staining and electron microscopy examination. Prior studies have shown an association between κ-light chain variable region germline gene use by the clonal plasma cells and the presence of MIDD. To assess the role of κ-light chain variable region germline gene usage in our patients, we amplified and sequenced the dominant κ-light chain variable germline gene in the baseline marrow cells of four patients using methods described previously.[19,20]

Treatment

All patients received initial therapy for multiple myeloma prior to undergoing their consolidation with HDM and auto-SCT. The goal of initial therapy in multiple myeloma is the achievement of a low tumor burden prior to the transplant. As the patients received their initial therapy in different centers, the treatment varied and is detailed in the Result section, treatment received. At the completion of the initial treatment, eligibility requirements for auto-SCT included total bilirubin <1.5 mg per 100 ml, liver transaminases level less than twice the upper limit of normal, left ventricular ejection fraction $>50\%$ and pulmonary diffusing capacity $>50\%$ of predicted, and absence of comorbidity that in the opinion of the treating physician would render the transplantation not advisable. All patients provided written informed consent and had PBSC products containing at least 2 million CD34+ cells per kg cryopreserved prior to transplantation. PBSC collection was performed using G-CSF 10 mcg/kg daily prior to leukapheresis for 10 days with or without preceding cyclophosphamide 3 g/m^2. HDM/auto-SCT was performed at an in-patient transplant unit. Patients received intravenous melphalan at 70 mg/m^2 for 2 days on days -3 and -2 and PBSC products were infused on day 0. Supportive care was administered as described previously. Toxicities were scored using National Cancer Institute clinical toxicity criteria.

Evaluation of response

Assessment of hematologic response to treatment was based on modified EORTC consensus criteria.[21] Patients were evaluated immediately before HDM/SCT (within a week) and were seen approximately every 3 months after HDM/auto-SCT and responses were scored at every visit. Complete response (CR) requires IF studies showing no evidence of the prior M-protein, normalization of the Free Light Chain Assay, a normal BM examination and no radiographic evidence of myeloma progression. Near complete response (nCR) requires disappearance of the M spike by serum protein electrophoresis but persistence of monoclonal band by IF. VGPR (very good partial response) requires a $>90\%$ reduction in the M-protein, and partial response (PR) a $>50\%$ reduction. Stable disease is defined as no change in the M-protein, whereas progression of disease is defined as recurrence of disease after CR or a $>25\%$ increase in M-protein from nadir.

The renal response to the administered therapy was also assessed based on pre- and post-HDM/auto-SCT levels of the serum creatinine, creatinine clearance, 24 h total protein, as well as recovery from dialysis dependency when applicable. However, it is important to caution that whereas the creatinine and the creatinine clearance always reflects the renal disease, proteinuria is not as useful. The degree of proteinuria at presentation does not correlate with the severity of the disease. Furthermore, although improvement in the proteinuria may reflect amelioration of the disease (like usually in the months following

HDM/auto-SCT), it can also be associated with worsening of the renal function due to the decrease in glomerular filtration.

Results

Patient characteristics

Patient characteristics are shown in Table 1. Six patients were male subjects; the median age was 50 (range 33–52). All fulfilled criteria for multiple myeloma. The median percentage of plasma cells in the BM was 21% (10–41%) and immunohistochemical staining for light chain isotype showed κ-clonality in all cases. Serum protein electrophoresis showed a monoclonal spike in one patient, whereas serum IF showed an IgG κ-monoclonal band in two patients. All seven patients, however, had elevated serum free κ-light chains and an abnormal κ-to- λ ratio with medians of 52.4 mg per 100 ml (5.3–385 mg per 100 ml) and 18.34 (3.01–203.7), respectively. The monoclonal protein deposited in the kidney consisted of free κ-light chains in all five patients with LCDD, κ-light chain and γ-heavy chain in the patient with LHCDD and intratubular crystals of κ-light chain in the patient with LCCDD and Fanconi syndrome. The median β2 microglobulin was 9.2 mg/l (2.3–18.4 mg/l) and the median serum albumin level 4.4 gm per 100 ml (3.5–4.6 mg/l). Using the ISS, five patients had stage III and two patients had stage I disease. All patients were stage IB by Durie–Salmon classification. Cytogenetic analysis in all seven patients and FISH analyses in three demonstrated no chromosomal aberrations.

All seven patients had hypertension that was controlled by antihypertensive medications. The patient with intracytoplasmic LCCDD presented with renal insufficiency (serum creatinine of 1.6 mg per 100 ml; creatinine clearance 40 ml/min) and Fanconi syndrome (with type II renal tubular acidosis and non-anion gap metabolic acidosis, glycosuria and aminoaciduria). The median serum creatinine was 4.6 (1.6–6.1), median creatinine clearance 35 ml/min (11–79 ml/min) and median 24-h proteinuria 4373 mg (237–8525 mg). Three patients (patients 1, 6 and 7) presented with severe acute renal failure necessitating initiation of dialysis within 2 weeks of initial presentation. These patients continued dialysis throughout the entire treatment including the transplant period.

Histopathologic findings on renal biopsy and κ-variable region germline gene use

All patients underwent a diagnostic renal biopsy. The five patients with LCDD and the single patient with LHCDD displayed a nodular sclerosing glomerulopathy with characteristic immunofluorescence profile and corresponding electron dense deposits. The glomerular capillary lumina were diffusely narrowed by mesangial expansion forming large nodules that stained strongly periodic acid-Schiff (PAS)-positive, trichrome-blue and weakly argyrophilic (Figure 1). There was variable thickening of glomerular basement membranes, Bowman's capsule, tubular basement membranes and vessel walls by PAS-positive material. These deposits typically formed ribbon-like, glassy thickenings of the tubular basement membranes, associated with

Table 1 Patients' clinical characteristics

Patients	*Renal diagnosis*	*Age*	*Sex*	*β2 MG (mg/l)*	*Alb*	*BM % PC*	*DS*	*ISS*	*SIF*	*SPEP (mg per 100 ml)*	*K/L ratio initial/ pre/post Auto-SCT*[a,b]	*Hematologic response pre/ post auto-SCT*[a]	*Creatinine (mg/dl) pre/post auto-SCT*[a]	*UTP (mg/dl) pre/post ASCT*[a]	*Dialysis pre/post ASCT*	*Renal allograft*
1	LCDD	42	M	18.4	4.4	12	I	III	N	N	17.8/0.92/0.48	CR/CR	7.6/1.5	1358/101	Yes/No	Yes
2	LCDD	33	M	5.8	3.5	26	I	III	IgG K	N	203/5.03/1.01	PR/CR	4.3/9	8525/3386	No/yes	No
3	LCDD	52	M	2.3	4.5	10	I	I	N	N	107/10.9/1.0	PR/uCR	2/1.7	3740/685	No/No	No
4	LCCDD	43	M	3.2	4.6	25	I	I	IgG K	800	171/50.2/6.14	PR/VGPR	1.7/1.8	5265/3535	No/No	No
5	LHCDD	51	M	9.2	3.9	16	I	III	N	N	3.01/0.60/0.38	CR/CR	7/3.5	4373/3889	No/No	No
6	LCDD	50	M	9.9	4.3	10	I	III	N	N	5.66/0.97/0.94	uCR/CR	6.5/3.9	237/0	Yes/Yes[c]	No
7	LCDD	51	F	16	4.6	41	I	III	N	N	7.25/2.13/0.92	PR/CR	5.3/1.2	6265/61	Yes/No	Yes

Abbreviations: Alb = albumin; β2 MG = β2-microglobulin; BM % PC = bone marrow plasmacytosis; DS = Durie–Salmon classification; ISS = International Staging System; K/L ratio = κ/λ ratio; K/L Ratio = serum free κ to λ ratio; LCCDD = light chain crystal deposition disease; LCDD = light chain deposition disease; LHCDD = light chain and heavy chain deposition disease; N = normal; PR = partial remission; SIF = serum immunofixation; SPEP = serum protein electrophoresis; uCR = unconfirmed complete remission (bone marrow examination not available); UTP = 24 h urine total protein; VGPR = very good partial remission (>90% reduction in monoclonal protein).

[a]Initial values were measured at initial diagnosis; Pre-auto-SCT values were measured within 1 week prior to auto-SCT; Post-auto-SCT values were measured approximately 3 months after auto-SCT.

[b]Normal K/L ratio: 0.26–1.65.

[c]This patient discontinued hemodialysis after HDM/auto-SCT after marked improvement in creatinine. He resumed peritoneal dialysis for symptomatic relief despite stable creatinine 2 months after HDM/auto-SCT. Discontinuation of peritoneal dialysis is currently being contemplated.

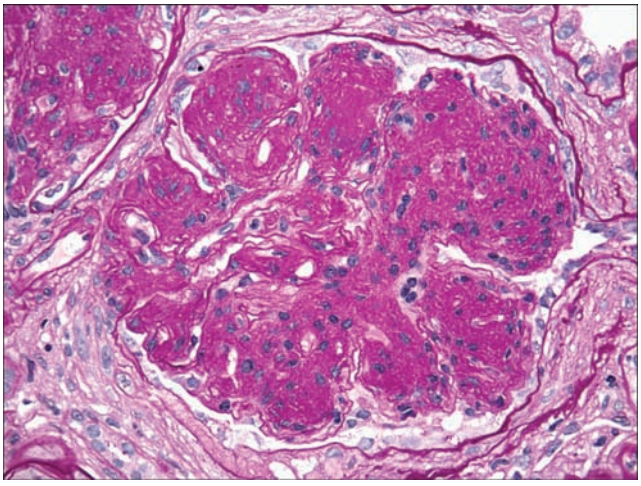

Figure 1 The glomerular mesangial regions are markedly and globally expanded by increased mesangial matrix and mild hypercellularity forming large nodules that narrow the capillary lumina. The nodules stain strongly periodic-acid Schiff (PAS)-positive. There is mild focal thickening of glomerular basement membranes (PAS, $\times 400$).

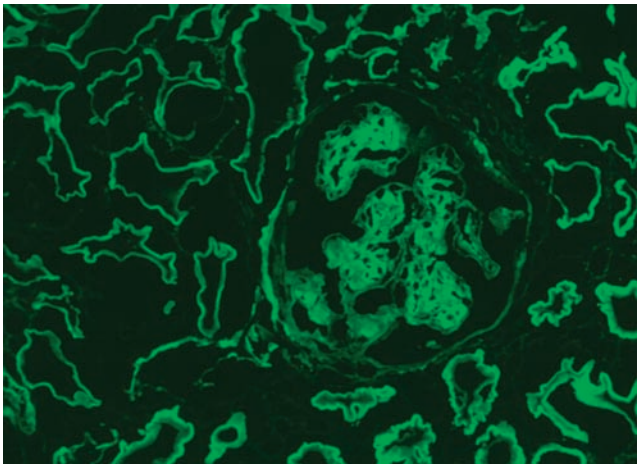

Figure 2 Immunofluorescence for κ-light chain reveals diffuse linear staining of the tubular and glomerular basement membranes, as well as positivity in the distribution of the mesangial nodules. A serial section stained for λ-light chain (not illustrated) was negative ($\times 100$).

focal tubular atrophy and interstitial fibrosis. One patient with LCDD also exhibited several atypical crystalline, lamellated casts of the myeloma type. In four patients, immunofluorescence studies showed intense and diffuse linear staining of all renal basement membranes and the mesangial nodules for κ-light chain, with negative staining for λ-light chain and Igs, consistent with κ-LCDD (Figure 2). One patient had strong linear staining for IgG and κ, with negative staining for λ, consistent with IgG κ-LHCDD. Electron microscopic examination typically showed expansion of mesangial areas with an increase in mesangial matrix forming large nodules containing finely granular mesangial electron dense deposits. Similar finely granular, electron-dense material formed linear band-like deposits involving the inner aspect of the glomerular basement membranes, the outer aspect of the tubular basement membranes and the areas surrounding the medial myocytes of arteries and arterioles (Figure 3).

In contrast to the patients with LCDD/LHCDD, microscopic examination of the patient with LCDD revealed no evidence of glomerular disease. The proximal tubular epithelial cells displayed irregular cytoplasmic expansion caused by abundant intracellular crystalline inclusions that deformed the cells. The intracytoplasmic crystals stained PAS-negative, trichrome-red and silver-negative. The proximal tubular cells displayed acute injury, including focal shedding of tubular cells into the tubular lumen, loss of brush border, luminal ectasia and regenerative nuclear atypia. In the medulla, a single atypical crystalline lamellated cast of the myeloma type was identified. Tubular atrophy and interstitial fibrosis affected 10% of the cortex. Immunofluorescence performed on pronase-digested paraffin sections showed intense diffuse staining for κ-light chain in the distribution of the proximal tubular intracellular crystals and the single atypical cast, with negative staining for λ-light chain. By electron microscopy, glomeruli were unremarkable and no electron dense deposits were identified involving renal basement membranes. Intracytoplasmic crystals were demonstrated

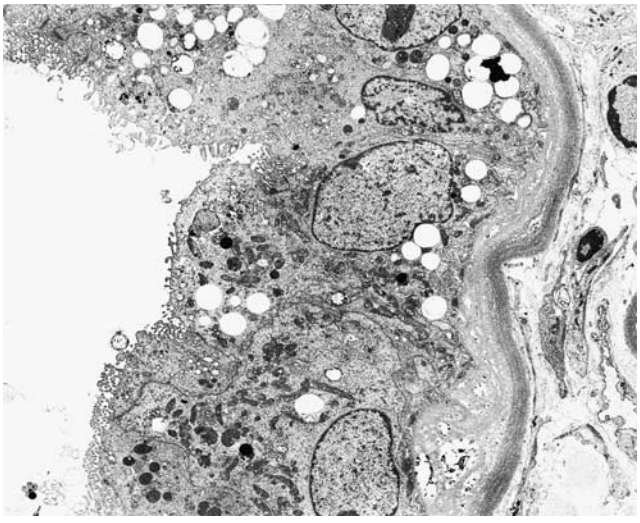

Figure 3 A representative tubular basement membrane shows finely granular linear deposits along the outer aspect of the tubular basement membrane, at the interstitial interface (electron micrograph, $\times 2000$).

in proximal tubular epithelial cells. The findings were interpreted as consistent with the special form of LCCDD known as κ-light chain Fanconi syndrome.

κ-light chain variable region germline genes were identified for three patients with LCDD and for the patient with κ-light chain Fanconi syndrome. The clones of two patients with LCDD used a VKI germline gene and the clone of the third used a VKII germline gene (DPK12). The joining region gene in these three cases was JK3. The clone of the patient with κ-light chain Fanconi syndrome used a VKIII germline gene (DPK21) with a JK4 joining region gene.

Treatment received and toxicity

The initial therapy prior to HDM/auto-SCT included thalidomide (escalated to 200 mg daily) and dexamethasone

in pulses (40 mg on days 1–4, 9–12 and 17–20) given for 3 cycles ($n=2$), dexamethasone pulses alone for 3 cycles ($n=3$), melphalan and dexamethasone for 5 cycles ($n=1$) and doxorubicin and dexamethasone for 2 cycles ($n=1$). Following initial therapy, five patients were mobilized with high-dose cyclophosphamide (3 gm/m^2) and G-CSF, and two with G-CSF alone (10 mcg/kg daily prior to leukapheresis for 10 days). All seven patients proceeded to HDM/auto-SCT and received melphalan as conditioning regimen at 140 mg/m^2 divided on days -3 and -2. Stem cells were infused on day 0. Patients received a mean of 5.8×10^6 CD34+ cells/kg ($3.6–8.3\times10^6$ CD34+ cells/kg).

HDM/auto-SCT was well tolerated. There was no mortality. All patients completed the planned treatment without major or unusual complications. Routine transfusion of blood products, prophylactic broad-spectrum antibiotics, hydration and analgesic medications for mucositis were administered to all patients. The non-hematologic adverse events included: neutropenic fever ($n=5$); mucositis requiring intravenous analgesic medication administered by PCA ($n=2$); nausea requiring antiemetics ($n=6$); transient rash ($n=2$); an episode of syncope attributed to dehydration ($n=1$); abdominal cramps of uncertain etiology ($n=1$). Three patients who were on dialysis prior to HDM/auto-SCT continued dialysis throughout the course of transplant. In these patients, melphalan was given after dialysis.

Response to therapy

At the completion of initial therapy, four patients had achieved a PR, two a CR and one a uCR (no BM biopsy available for confirmation of CR in this patient). Six of the seven patients achieved a hematologic CR after HDM/auto-SCT. The patient with LCCDD achieved a VGPR as reflected by persistence of low level free κ-chain in the serum (that is, >90% reduction in the level of free κ-light chain). This patient showed evidence of hematologic progression 8 months after transplant. He is currently being evaluated for a second auto-SCT followed by auto-SCT from an HLA-matched sibling. With a median follow-up time of 23.6 months (range 7.9–69.8 months), all other patients remain in hematologic CR.

Among the four patients who were dialysis independent at the time of HDM/auto-SCT, the serum creatinine has improved in two (patients 3 and 5), remained stable in one (patient 4) who achieved hematologic PR) and worsened in one (patient 2), leading to hemodialysis despite hematologic CR (Figure 4). Proteinuria has improved significantly in the four patients shortly after HDM/auto-SCT (Table 1). However, we should caution that although an improvement in the proteinuria may reflect improvement of the renal function, (as shortly after HDM/auto-SCT as shown in Table 1), it may also reflect worsening of the disease due to a decrease in the glomerular filtration, as exemplified by patient 2 whose proteinuria continued to improve despite worsening in his creatinine clearance. The three patients who were dialysis-dependent at the time of HDM/auto-SCT achieved hematologic CR. Two of them have undergone kidney transplantation 14.1 and 45.7 months after HDM/auto-SCT (patients 1 and 7), and have a normal creatinine clearance 35.9 and 69.8 months after HDM/auto-SCT. The kidney transplantation was deemed reasonable in these patients as they had achieved a hematologic CR and had no comorbid condition otherwise. The third patient (patient 6) who also remains in hematologic CR became dialysis independent after HDM/auto-SCT for a period of 2 months following improvement in his creatinine, but has resumed peritoneal dialysis mainly for symptomatic relief (nausea) and despite a stable creatinine. Discontinuation of his peritoneal dialysis is currently being contemplated (Figure 4).

Discussion

Monoclonal Ig deposition disease is a rare condition and its management is controversial. We report our experience using high-dose chemotherapy and SCT in patients with MIDD, showing a significant benefit with this treatment modality. All patients who underwent HDM/auto-SCT, including five with LCDD, one with LHCDD and one with LCCDD, had excellent hematologic responses. Six of the seven patients achieved durable CRs whereas the seventh achieved a very good PR. As kidney dysfunction represents the most prominent morbidity in MIDD, it is important to emphasize that the elevated serum creatinine was ameliorated in five out of seven patients after HDM/auto-SCT—albeit in two of them with the use, ultimately, of kidney transplantation—and remained stable in one. With a median follow up of 23.6 months, only one of the seven patients in our series has had worsening of kidney function after an initial improvement (and despite a sustained hematologic response). This patient is being considered for kidney transplantation. All patients received melphalan at 140 mg/m^2, a dose that was well tolerated. There was no transplant-related mortality and no worsening of kidney function during the peri-transplant period.

This experience is in keeping with prior reports that have described an important role for HDM/auto-SCT in patients with MIDD. Weichman and co-workers described six patients, five with LCDD and one with LCCDD, who were treated with HDM/auto-SCT and who achieved a good outcome with acceptable and expected toxicity.[16] As described in the present report, most patients had complete hematologic remission followed by renal improvement and reversal of dialysis dependence in one case. Royer *et al*.[14] have reported their experience in 11 patients with LHCDD who received a variety of therapeutic regimens. They also observed an overall favorable outcome, including complete hematologic remission in five patients with improvement of kidney function in four[14] and several patients with cardiac and/or hepatic involvement who experienced functional improvement after SCT. More recently, Lorenz and co-workers reported the long-term outcome after auto-SCT of six patients. Although one patient did not survive the procedure, five had a hematologic response by standard criteria and four who were not on dialysis at the time of transplantation had a renal response as assessed by improvement in their glomerular filtration rate.[22] Thus, our experience further highlights the potentially important role of SCT in MIDD, in striking contrast to the minimal

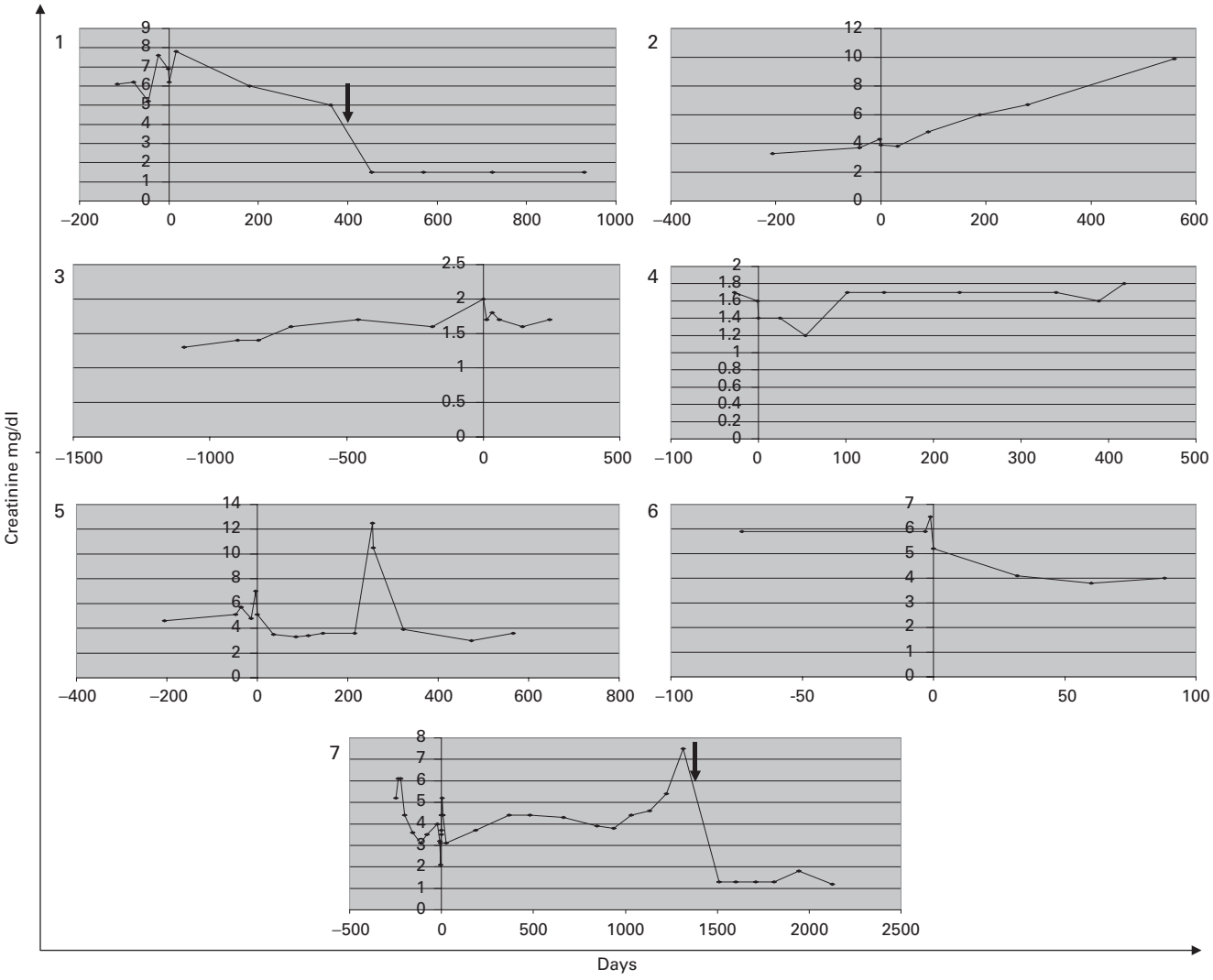

Figure 4 Progression of creatinine in seven patients before and after auto-SCT (time zero on the *x* axis). The downward arrows indicate kidney transplantation. Patient no. 5 had a transient and reversible worsening of creatinine due to an episode of severe dehydration caused by gastroenteritis.

benefit when conventional chemotherapy (including melphalan and prednisone) is used in these patients.

All patients in our series had early stage multiple myeloma (stage IB Durie–Salmon) with significant renal dysfunction. The presence of κ-light chain deposits by immunofluorescence and electron microscopy, and the typical VK germline gene use pattern, indicate that there is a specific tropism for features of the renal landscape in this disease. It is likely that these patients are diagnosed at an earlier stage compared to other patients with multiple myeloma because of the high propensity of their light chain to cause renal damage, even at low serum levels. This hypothesis would account for the inability to detect the presence of a serum paraprotein in a significant percentage of patients with MIDD previously reported in the literature. With the availability of the Serum Free Light Chain Assay, most patients with MIDD should have detectable serum paraprotein as shown in this report, despite negative serum protein electrophoresis and serum immunofixation (SIF).

As a corollary, it is likely that the excessive renal toxicity of free light chains in MIDD also implies that even low levels of circulating free light chains may have deleterious renal consequences. Hence, one of the aims of therapy should be to suppress the free light chain production to the greatest extent. The success of HDM/auto-SCT in curbing renal dysfunction may depend on achieving complete hematologic remission. In this context, maintenance therapy after HDM/auto-SCT and tandem HDM/auto-SCT for patients who do not achieve a CR after first transplantation may be options worth investigating in patients with MIDD. Indeed, maintenance therapy using new therapeutic agents like thalidomide[23–25] and tandem HDM/auto-SCT[26] have both been shown to increase the rate of complete hematologic remission, prolong time to disease progression and overall survival in patients with multiple myeloma. Although it remains an open question, in our opinion, it is likely that these approaches aiming at achieving a durable complete hematologic remission may be of special benefit to these patients.

The use of renal transplantation in patients with MIDD has been controversial. Experts have reached opposing conclusions as most available data have been anecdotal and pertain to retrospective analyses.[27–31] The main argument against the use of kidney allografting in MIDD is based on the risk of recurrence in the allograft as well as the overall poor prognosis because of the underlying hematologic malignancy. However, there is little information in these reports regarding the hematologic response of patients prior to kidney transplantation. With the advent of newer treatment modalities for clonal plasma cell dyscrasias, including auto-SCT, this subject needs to be revisited. There is only one report in the literature on sequential auto-SCT and kidney transplantation in MIDD. In that report, the patient's creatinine remained at a level of 1.7 mg per 100 ml for 26 months after renal transplantation, and a kidney biopsy showed no recurrence of MIDD, despite hematologic partial response after HDM/auto-SCT.[31] In the series presented here, two patients achieved complete hematologic remission after HDM/auto-SCT and subsequently underwent renal transplantation from a living related donor, became dialysis independent and remain so after a relatively long follow-up. These cases argue that renal allograft may be a reasonable option for MIDD patients with renal failure and dialysis dependence, who have achieved a hematologic CR. With advances in the treatment of myeloma and the higher hematologic CR rate following single or tandem HDM/auto-SCT and other new therapies, the decision regarding kidney transplantation in MIDD deserves further scrutiny.

In summary, we report our experience with the use of HDM/auto-SCT in patients with MIDD, an experience that corroborates previous reports claiming significant benefits. Renal dysfunction including dialysis dependence can be reversed or stabilized with HDM/auto-SCT with or without subsequent renal transplantation. The goal of successful therapy may hinge on the complete suppression of light chain production. Further benefit in patients achieving less than a CR after a single HDM/auto-SCT may be provided by the use of novel agents, post transplant maintenance therapy or tandem HDM/auto-SCT. Multicenter studies will be needed to address these questions.

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References

1 Pozzi C, D'Amico M, Fogazzi GB, Curioni S, Ferrario F, Pasquali S *et al*. Light chain deposition disease with renal involvement: clinical characteristics and prognostic factors. *Am J Kidney Dis* 2003; **42**: 1154–1163.
2 Buxbaum J, Gallo G. Nonamyloidotic monoclonal immunoglobulin deposition disease. Light-chain, heavy-chain, and light- and heavy-chain deposition diseases. *Hematol Oncol Clin North Am* 1999; **13**: 1235–1248.
3 Buxbaum JN, Genega EM, Lazowski P, Kumar A, Tunick PA, Kronzon I *et al*. Infiltrative nonamyloidotic monoclonal immunoglobulin light chain cardiomyopathy: an underappreciated manifestation of plasma cell dyscrasias. *Cardiology* 2000; **93**: 220–228.
4 Croitoru AG, Hytiroglou P, Schwartz ME, Saxena R. Liver transplantation for liver rupture due to light chain deposition disease: a case report. *Semin Liver Dis* 2006; **26**: 298–303.
5 Popovic M, Tavcar R, Glavac D, Volavsek M, Pirtosek Z, Vizjak A. Light chain deposition disease restricted to the brain: The first case report. *Human Pathol* 2007; **38**: 179–184.
6 Toor AA, Ramdane BA, Joseph J, Thomas M, O'Hara C, Barlogie B *et al*. Cardiac nonamyloidotic immunoglobulin deposition disease. *Mod Pathol* 2006; **19**: 233–237.
7 Pozzi C, Locatelli F. Kidney and liver involvement in monoclonal light chain disorders. *Semin Nephrol* 2002; **22**: 319–330.
8 Michopoulos S, Petraki K, Petraki C, Dimopoulos MA. Light chain deposition disease of the liver without renal involvement in a patient with multiple myeloma related to liver failure and rapid fatal outcome. *Dig Dis Sci* 2002; **47**: 730–734.
9 Terashima K, Takahashi K, Kojima M, Imai Y, Tsuchida S, Migita S *et al*. Kappa-type light chain crystal storage histiocytosis. *Acta Pathol Jpn* 1978; **28**: 111–138.
10 Lin J, Markowitz GS, Valeri AM, Kambham N, Sherman WH, Appel GB *et al*. Renal monoclonal immunoglobulin deposition disease: the disease spectrum. *J Am Soc Nephrol* 2001; **12**: 1482–1492.
11 Dhodapkar MV, Merlini G, Solomon A. Biology and therapy of immunoglobulin deposition diseases. *Hematol Oncol Clin North Am* 1997; **11**: 89–110.
12 Heilman RL, Velosa JA, Holley KE, Offord KP, Kyle RA. Long-term follow-up and response to chemotherapy in patients with light-chain deposition disease. *Am J Kidney Dis* 1992; **20**: 34–41.
13 Firkin F, Hill PA, Dwyer K, Gock H. Reversal of dialysis-dependent renal failure in light-chain deposition disease by autologous peripheral blood stem cell transplantation. *Am J Kidney Dis* 2004; **44**: 551–555.
14 Royer B, Arnulf B, Martinez F, Roy L, Flageul B, Etienne I *et al*. High dose chemotherapy in light chain or light and heavy chain deposition disease. *Kidney Int* 2004; **65**: 642–648.
15 Sakakima M, Fujigaki Y, Tsuji T, Fukasawa H, Miyaji T, Naito K *et al*. High dose chemotherapy and stem cell support in a patient of light- and heavy-chain deposition disease with abnormal marrow cell surface antigens and no monoclonal protein. *Intern Med* 2005; **44**: 970–974.
16 Weichman K, Dember LM, Prokaeva T, Wright DG, Quillen K, Rosenzweig M *et al*. Clinical and molecular characteristics of patients with non-amyloid light chain deposition disorders, and outcome following treatment with high-dose melphalan and autologous stem cell transplantation. *Bone Marrow Transplant* 2006; **38**: 339–343.
17 Salant DJ, Sanchorawala V, D'Agati VD. A case of atypical light chain deposition disease—diagnosis and treatment. *Clin J Am Soc Nephrol* 2007; **2**: 858–867.
18 Greipp PR, San Miguel J, Durie BG, Crowley JJ, Barlogie B, Blade J *et al*. International staging system for multiple myeloma. *J Clin Oncol* 2005; **23**: 3412–3420.

19 Comenzo RL, Wally J, Kica G, Murray J, Ericsson T, Skinner M *et al*. Clonal immunoglobulin light chain variable region germline gene use in AL amyloidosis: association with dominant amyloid-related organ involvement and survival after stem cell transplantation. *Br J Haematol* 1999; **106**: 744–751.
20 Comenzo RL, Zhang Y, Martinez C, Osman K, Herrera GA. The tropism of organ involvement in primary systemic amyloidosis: contributions of Ig V(L) germ line gene use and clonal plasma cell burden. *Blood* 2001; **98**: 714–720.
21 Blade J, Samson D, Reece D, Apperley J, Bjorkstrand B, Gahrton G *et al*. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. *Br J Haematol* 1998; **102**: 1115–1123.
22 Lorenz EC, Gertz MA, Fervenza FC, Dispenzieri A, Lacy MQ, Hayman SR *et al*. Long-term outcome of autologous stem cell transplantation in light chain deposition disease. *Nephrol Dial Transplant* 2008; **23**: 2052–2057.
23 Attal M, Harousseau JL, Leyvraz S, Doyen C, Hulin C, Benboubker L *et al*. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. *Blood* 2006; **108**: 3289–3294.
24 Brinker BT, Waller EK, Leong T, Heffner Jr LT, Redei I, Langston AA *et al*. Maintenance therapy with thalidomide improves overall survival after autologous hematopoietic progenitor cell transplantation for multiple myeloma. *Cancer* 2006; **106**: 2171–2180.
25 Abdelkefi A, Ladeb S, Torjman L, Ben Othman T, Lakhal A, Ben Romdhane N *et al*. Single autologous stem cell transplantation followed by maintenance therapy with thalidomide is superior to double autologous transplantation in multiple myeloma: results of a multicenter randomized clinical trial. *Blood* 2007; **111**: 1805–1810.
26 Attal M, Harousseau JL, Facon T, Guilhot F, Doyen C, Fuzibet JG *et al*. Single versus double autologous stem-cell transplantation for multiple myeloma. *N Engl J Med* 2003; **349**: 2495–2502.
27 Leung N, Lager DJ, Gertz MA, Wilson K, Kanakiriya S, Fervenza FC. Long-term outcome of renal transplantation in light-chain deposition disease. *Am J Kidney Dis* 2004; **43**: 147–153.
28 Taheri D, Chehrei A, Fesharakizadeh M, Seyrafean S, Shahidi S, Emami A *et al*. Recurrent multiple myeloma following renal transplantation: a case report. *Transplant Proc* 2007; **39**: 1063–1065.
29 Alchi B, Nishi S, Iguchi S, Shimotori M, Sakatsume M, Ueno M *et al*. Recurrent light and heavy chain deposition disease after renal transplantation. *Nephrol Dial Transplant* 2005; **20**: 1487–1491.
30 Short AK, O'Donoghue DJ, Riad HN, Short CD, Roberts IS. Recurrence of light chain nephropathy in a renal allograft. A case report and review of the literature. *Am J Nephrol* 2001; **21**: 237–240.
31 Barraclough KA, Dowling JP, Schwarer AP, Perry GJ. Sequential autologous peripheral blood stem cell transplantation and kidney transplantaion of light chain deposition disease. *Nephrol Dial Transplant* 2007; **22**: 1268–1269.