High dose chemotherapy in light chain or light and heavy chain deposition disease

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Background. Conventional chemotherapy for myeloma yield unsatisfactory results in light and/or heavy chain deposition disease [(H)CDD] Because of the well-established dose-response effect of high dose melphalan in multiple myeloma, aiming to dramatically reduce the pathogenic monoclonal immunoglobulin (MIg) level, high dose therapy is a tempting alternative approach.

Methods. We treated 11 young patients with L(H)CDD by high dose therapy with the support of autologous blood stem cell transplantation. All had renal symptoms, including four who required dialysis and seven who had various, mainly cardiac, extrarenal manifestations.

Results. No toxic deaths occurred. A decrease in the MIg level was observed in eight patients, with complete disappearance from serum and urine in six cases. Improvement in manifestations related to MIg deposits were observed in six patients, including renal, cardiac, and hepatic responses in 4/11, 4/4, and 2/2 cases, respectively. Histologic regression of MIg deposits was documented in cardiac, hepatic, and skin biopsies. In contrast, examination of the kidney still showed light chain deposits in one patient who had renal transplantation 3 years after high dose therapy, at a time when he was in persisting remission.

Within a median follow-up of 51 months, three patients were retreated because of multiple myeloma relapse, of whom one died and one required hemodialysis, and renal function secondarily deteriorated in a patient who had resistant multiple myeloma. Otherwise, no manifestations related to MIg deposits occurred or recurred in any patient.

Conclusion. Present results of this retrospective study argue in favor of a benefit of high dose therapy with stem cell support in young patients with L(H)CDD.

Monoclonal immunoglobulin (MIg) deposition in tissue may occur either as Congo red binding fibrils, in AL amyloidosis, or as amorphous, nonfibrillar deposits in light and/or heavy chain deposition diseases [L(H)CDD] [1]. First reported in 1973 [abstract; Antonovych T, et al, Lab Invest 30:370A, 1974], L(H)CDD was definitely characterized in 1976 by Randall et al [2] who recognized the systemic nature of the disease. Renal involvement is a constant feature of L(H)CDD and renal manifestations often dominates the clinical presentation. Proteinuria is often an early finding, rapidly followed by renal failure, the high prevalence, early appearance, and severity of which is remarkable [3]. In addition to the kidney, light and/or heavy chain [L(H)C] deposition may involve other organs, particularly the heart and the liver where it can be totally asymptomatic or cause life-threatening damage. This explains, at least in part, why the survival time from onset of symptoms varies from a few months to 10 years [4].

L(H)CDD results from the deposition of monotypic immunoglobulin (Ig) chains along basement membranes. Nodular glomerulosclerosis is the most characteristic pathologic renal feature. Immunofluorescence examination is a key step in the diagnosis, showing monotypic deposition of light chain (or heavy chain) along glomerular and, more important, tubular basement membranes [3]. Monotypic Ig chains are produced by a monoclonal B-cell clone, the burden of which may be variable. It may be associated with multiple myeloma or other lymphoproliferative disease, but many patients have no evidence of any overt plasma cell dyscrasia and the presence of a serum or urine monoclonal Ig component cannot be established in some of them [1, 4].

Even in the latter cases, present treatment is based on eliminating the clonal plasma cells responsible for the production of the deposited protein. Using conventional chemotherapy, this approach benefits only a minority of patients [4]. Because of the well-established dose-response effect of melphalan in myeloma patients [5], high dose therapy is an alternative tempting approach, although it appears challenging owing to the renal
and cardiac dysfunction that commonly occurs in patients with L(H)CDD. However, recent advances in supportive care and the availability of growth factors and mobilized stem cells have reduced the morbidity and mortality of high dose therapy, including in patients with renal dysfunction [6, 7]. This prompted us to attempt high dose therapy, with the support of autologous stem cell transplantation, in patients with L(H)CDD. We report our experience of this therapeutic approach in 11 patients.

**METHODS**

We retrospectively reviewed all patients with L(H)CDD who were treated by high dose therapy and autotransplantation in our department. The first (N = 4) were treated in the early 1990s with encouraging results, particularly in one case [8]. Therefore, since 1995, we decided to treat by high dose therapy all patients with L(H)CDD, whatever their renal function, provided they were under 65 years of age, had a relatively good performance status (OMS index ≤ 2) and gave informed consent. Between 1995 and 1999, we saw seven patients who met these criteria. All were included in this study, in addition to the initial four.

In all 11 patients, L(H)CDD was diagnosed by means of renal biopsy, according to accepted criteria, including immunofluorescence data demonstrating nonamyloid monotypic light chain and/or heavy chain deposition in renal parenchyma, particularly along tubular basement membranes [3]. Specific stainings for amyloid deposits were performed in all cases.

Serum and urine protein immunofixation (or immunoelectrophoresis), skeletal x-ray films and at least one bone marrow aspiration were performed in all patients. The diagnosis of multiple myeloma was considered when at least 5% of unequivocally dystrophic plasma cells were seen on bone marrow smears and/or when obvious lytic bone lesions were detected on x-ray films. Multiple myeloma stages were defined according to the Durie and Salmon staging system [9]. Briefly, stage I was characterized by relatively low monoclonal protein serum and urine concentrations, normal calcemia, and absence of anemia and of bone lesions. Stage III multiple myeloma was considered when multiple bone lesions, high monoclonal protein concentration, hypercalcemia, and/or a hemoglobin serum level of less than 10 g/dL were observed. Patients who do not fulfill the criteria for stage I or stage III were classified as stage II. In the absence of these abnormalities and of more than 5% of dystrophic plasma cells on bone marrow smears, patients were considered to have a monoclonal gammopathy of undetermined significance, although atypical because of the M Ig deposit-related organ manifestations (“MGUS”).

**TREATMENT**

In all cases, autologous blood stem cells (ABSC) were collected at diagnosis. The mobilization procedure and subsequent therapeutic protocol varied according to the period of time (before and after 1995).

In the four patients treated before 1995, ABSC were mobilized by chemotherapy alone (cyclophosphamide 4 g/m²). Thereafter, patients received three to six monthly courses of a standard dose chemotherapeutic regimen, most often a vincristine, adriblaotine, dexamethasone (VAD)-like regimen [combining continuous 24-hour-infusion of vincristine (0.4 mg/day) and doxorubicin (9 mg/m²/day) with intravenous methylprednisolone (400 mg/day) for 4 days]. In three cases, high dose therapy was performed according to a previously described protocol combining melphalan 140 mg/m², cyclophosphamide 60 mg/kg, CCNU and VP16 with a 12 gray total body irradiation (TBI) [10]. The last patient did not receive TBI but a combination of melphalan 140 mg/m² (given as a single 2-hour perfusion) and oral busulfan (4 mg/kg/day × 3 days).

In the seven following patients, ABSC mobilization was performed using granulocyte-colony-stimulating factor (G-CSF) (10 µg/kg/day × 4 days). For these seven patients, no standard dose chemotherapy was administered between ABSC collection and high dose therapy. Pretreatment cytoreduction used high dose melphalan alone (140 mg/m² (N = 6) or 200 mg/m² (N = 1) given as a single 2-hour perfusion on day 2). Two tandem courses of melphalan 140 mg/m² separated by 3 to 5 months were performed in two patients. ABSC were reinfused at day 0 and all patients received G-CSF (5 µg/kg/day) from day 6 posttransplant until the absolute neutrophil count was greater than 1.0 × 10⁹/L.

In all cases, graft content of hematopoietic progenitors was assessed numerating CD34-positive cells. All high dose therapy regimens were supported by the reinfusion of at least 2 × 10⁶/kg CD34-positive cells. High dose therapy and autotransplantation were performed in a protected unit. Supportive care was given as needed and included blood products and broad-spectrum antibiotics. Patients requiring renal replacement therapy were dialyzed prior to high dose melphalan infusion and then 72 hours later; otherwise, their hemodialysis schedule was unchanged, at three times a week throughout the transplant period.

The response to treatment was monitored clinically and by means of serum and urine immunoglobulin studies. Complete immunochemical remission was defined by the disappearance of M Ig on immunofixation studies of serum and urine. A very good response was considered when a reduction of 75% or more in the M Ig level was observed. Improvement in clinical manifestations related to L(H)C deposits was assessed on the basis of the
following criteria adapted from those described by Gertz et al in AL amyloidosis [11]: resolution of symptoms of congestive heart failure with improved echocardiography; reduction in the size of the liver by more than 2 cm (with normalization of serum alkaline phosphatase); improvement in renal function; and at least a 50% decrease in the 24-hour urinary protein excretion associated with a serum albumin level reincrease, in the absence of proteinuria and renal failure. Proteinuria was found in ten patients, including three with nephrotic syndrome (urine protein >3 g/day and serum albumin <30 g/L). Renal failure was present in nine patients of whom four experienced rapid deterioration of renal function and required definitive dialysis. The five other patients initially had mild renal insufficiency with serum creatinine levels ranging between 170 and 300 μmol/L.

Extrarenal manifestations were cardiac (N = 7), hepatic (N = 2), and neurologic (N = 1). Five patients had two involved organs and two patients had three or more involved organs. The two patients with symptoms due to liver deposits had hepatomegaly and mild increase in serum alkaline phosphatase level. Heart involvement dominated the clinical presentation in four patients who had congestive heart failure in combination with echocardiographic signs suggestive of Ig deposits (increased thickness of interventricular septum, abnormal myocardial texture, and decreased systolic ventricular function). In three other patients, of whom two experienced arrhythmia episodes and one had no cardiac symptoms, ultrasound examination of the heart showed abnormalities suggestive of cardiac deposits. One patient had central nervous system manifestations, including facial palsy and endocrine dysfunction of central origin (hypothyroidism, adrenal insufficiency, diabetes insipidus, and hypogonadism). In addition, the patient had a massive protein increase in cerebrospinal fluid (8 g/L containing monoclonal κ light chain) without associated hypercellularity.

Light microscopy and immunofluorescence studies of renal biopsies showed glomerular and tubular lesions characteristic of L(H)CDD in all patients. Nine had only light chain deposits with predominance of κ isotype (N = 7) as compared to λ isotype (N = 2). In the two remaining patients, deposits were composed of κ light chain associated with γ heavy chain. In one case, a typical pattern of κLCDD was combined with small Congo red–positive deposits.

In the two patients with symptomatic liver involvement, hepatic biopsy showed light chain deposits confined to sinusoids and basement membranes of biliary ductules without associated parenchymal lesions. Two patients, one with heart failure and the other with nonsymptomatic echocardiographic abnormalities, had myocardial biopsy showing monotypic deposits in the vascular walls and perivascular areas of the heart. Immunofluorescence studies of skin biopsy samples were performed in nine patients and disclosed monotypic Ig deposits of variable localization, most often at the dermoepidermal junction, in six cases. Congo red staining was negative in all cases except in that patient with both renal κLCDD and amyloidosis in whom cutaneous studies also suggested the combination of the two types of deposits.

A monoclonal Ig was detected in the serum and/or urine of ten patients. Isotypes were IgGκ (N = 3), IgGλ (N = 1), IgDκ (N = 1), and κ light chain only (N = 5). One patient with κ light chain renal deposits and hypogammaglobulinemia had no monoclonal Ig detectable in serum and urine. Ten patients had overt multiple myeloma, seven of whom had stage I disease and three had stage III disease, according to the Durie and Salmon classification.

### Table 1. Patients’ characteristics at beginning of treatment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (range)</th>
</tr>
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<tbody>
<tr>
<td>Number of patients</td>
<td>11</td>
</tr>
<tr>
<td>Median age years (range)</td>
<td>42 (35–65)</td>
</tr>
<tr>
<td>Sex M/F</td>
<td>7/4</td>
</tr>
<tr>
<td>Clinical manifestations</td>
<td></td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>3</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td></td>
</tr>
<tr>
<td>Creatinine &gt; 200 μmol/L</td>
<td>5</td>
</tr>
<tr>
<td>Dialysis</td>
<td>4</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>4</td>
</tr>
<tr>
<td>Hepatomegaly + cholestasis</td>
<td>2</td>
</tr>
<tr>
<td>Neurologic symptoms and endocrinopathy</td>
<td>1</td>
</tr>
<tr>
<td>Number of organs involved</td>
<td></td>
</tr>
<tr>
<td>&lt;2 clinical manifestations</td>
<td>4</td>
</tr>
<tr>
<td>≥2 clinical manifestations</td>
<td>5</td>
</tr>
<tr>
<td>≥3 clinical manifestations</td>
<td>2</td>
</tr>
<tr>
<td>Monoclonal protein</td>
<td></td>
</tr>
<tr>
<td>IgGκ</td>
<td>3</td>
</tr>
<tr>
<td>IgGλ</td>
<td>1</td>
</tr>
<tr>
<td>IgDκ</td>
<td>1</td>
</tr>
<tr>
<td>Light chain κ only</td>
<td>5</td>
</tr>
<tr>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>Myeloma</td>
<td>10</td>
</tr>
<tr>
<td>Stage I</td>
<td>7</td>
</tr>
<tr>
<td>Stage III</td>
<td>3</td>
</tr>
<tr>
<td>MGUS*</td>
<td>1</td>
</tr>
<tr>
<td>Median time from diagnosis to ABSCT months</td>
<td>7 (3–48)</td>
</tr>
</tbody>
</table>

*ABSCT is autologous blood stem cell transplant.

*Two patients received transient dialysis during ABSCT mobilization.

*Facial palsy, hyperproteinorachia, pan-hypopituitarism.

RESULTS

Patients’ characteristics

Table 1 summarizes the main data from the 11 patients. There were four women and seven men. Their median age was 42 years (range 35 to 65 years). Median time from first symptoms to high dose therapy was 7 months (range 3 to 48 months).

At presentation, all patients had renal symptoms, mostly proteinuria and renal failure. Proteinuria was found in ten patients, including three with nephrotic syndrome (urine protein >3 g/day and serum albumin <30 g/L). Renal failure was present in nine patients of whom four experienced rapid deterioration of renal function and required definitive dialysis. The five other patients initially had mild renal insufficiency with serum creatinine levels ranging between 170 and 300 μmol/L.
Treatment and treatment-related toxicity

All patients in whom ABSC were mobilized using chemotherapy had febrile neutropenia. Two of these, who at presentation had a serum creatinine level of 80 and 250 μmol/L, experienced acute renal failure during bacterial sepsis complicating the chemotherapy-induced aplasia. Both required transient dialysis for 1 and 12 weeks, respectively. When performed after G-CSF alone, ABSC mobilization and collection were well tolerated. A single mobilization procedure, followed by one to four leukaphereses, allowed to collect an adequate number of CD34-positive cells in all patients but one, who had to be mobilized twice.

No toxic death occurred either during ABSC mobilization and collection or during high dose therapy and auto-transplantation. Three of the four patients who received high dose mephalan while on hemodialysis developed cerebral and/or cardiac complications. Two had episodes of atrial fibrillation and two developed severe encephalopathy with generalized tonic-clonic seizures and coma, one of these after treatment by mephalan 200 mg/m². In both, causes of coma such as infections, metabolic disturbances, cerebral ischemia, or hemorrhage were excluded. Both patients recovered but mechanical ventilation was needed for 2 weeks in the one who had central nervous system involvement due to LCDD. In contrast, one hemodialyzed patient received sequential high dose therapy and tandem transplant with no significant complications.

Two of the seven patients with no or mild renal insufficiency pretransplant developed transient moderate deterioration of renal function during the aplasia consecutive to high dose therapy. Hematopoietic recovery was satisfactory in all patients, with a median number of 13 and 14 days to reach more than $1 \times 10^9$/L granulocytes and more than $25 \times 10^9$ platelets, respectively. These features were similar in patients with or without end-stage renal failure. All patients returned home within a median time of 18 days (range 13 to 130 days) after transplantation.

Response to therapy

High dose therapy and autotransplantation produced a decrease in the level of MIg in eight of the ten patients who initially had a detectable monoclonal gammopathy. Six patients (four of seven and two of three with stage I and stage III multiple myeloma, respectively) achieved complete immunological remission and two patients were considered very good responders.

Improvement in manifestations related to L(H)C deposits were observed in six patients, five of whom had achieved a complete immunological response and one a very good one (Table 2). According to previously described criteria, cardiac, hepatic, and renal responses were observed in four of four, two of two, and four of 11 cases, respectively. In addition, a neurologic response occurred in one patient.

All four patients who initially had congestive heart failure had resolution of clinical symptoms of heart involvement, complete in three of them. Echocardiogram improved in five of the seven cases with initial abnormalities and the two patients who had arrhythmic episodes did not experience recurrence. Reduction in the size of the liver by more than 2 cm and normalization of serum alkaline phosphatase was observed in the two patients with hepatic manifestations. The patient with neurologic and endocrine symptoms experienced a marked improvement in facial palsy and encephalopathy, associated with a decrease in cerebrospinal fluid protein level (from 8 g/L at transplantation to 1 g/L 3 months posttransplant), but

### Table 2. After high dose therapy visceral improvement in patients in complete (or near complete) response

<table>
<thead>
<tr>
<th>Kidney</th>
<th>Heart</th>
<th>Miscellaneous</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Still requiring dialysis</td>
<td>Improved&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Improvement in liver&lt;sup&gt;e&lt;/sup&gt; and neurologic manifestations&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Alive (36 months +) Relapse (24 months)</td>
</tr>
<tr>
<td>2 Still requiring dialysis</td>
<td>No more arrhythmic Episodes</td>
<td></td>
<td>Alive in CR (25 months +)</td>
</tr>
<tr>
<td>3 Resolution of nephrotic syndrome; creatinine level (300 → 160 μmol/L)</td>
<td>Improved&lt;sup&gt;d,e&lt;/sup&gt;</td>
<td>Improvement in hepatic manifestations&lt;sup&gt;d,e&lt;/sup&gt;</td>
<td>Relapse (44 months) Dead (85 months) Alive in CR (50 months)</td>
</tr>
<tr>
<td>4 Renal transplant (36 months after high dose therapy)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 Creatinine level (250 → 80 μmol/L)</td>
<td>Improved&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td>Alive (88 months +) Relapse (30 months) Dialysis (74 months)</td>
</tr>
<tr>
<td>6 Resolution of nephrotic syndrome; creatinine level (260 → 110 μmol/L)</td>
<td>Improved&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td>Alive in CR (65 months +)</td>
</tr>
</tbody>
</table>

<sup>a</sup>CR is complete remission.
<sup>b</sup>See also Table 3.
<sup>c</sup>Resolution of symptoms of congestive heart failure with improved echocardiography.
<sup>d</sup>Reduction in the size of the liver by more than 2 cm (with normalization of serum alkaline phosphatase).
<sup>e</sup>Improved in facial palsy and encephalopathy, decrease in cerebrospinal fluid level protein.
<sup>f</sup>Histological regression of L(H)C deposits.
no improvement in endocrine dysfunction. In the seven patients who died, not needing permanent dialysis, six had an increased creatinine level before high dose therapy; the creatinine was unchanged in two and improved by 50% to 75% 1 year posttherapy in four. The nephrotic syndrome disappeared in three of three patients (see Tables 2 and 3).

Histologic regression of L(H)C deposits was documented in the cardiac ($N=1$) and hepatic ($N=1$) biopsies performed 1 year after high dose therapy. In addition, complete disappearance of skin L(H)C deposits was observed in four of the five patients in whom immunofluorescence studies on skin biopsy samples were repeated (Fig. 1). Of note, in the patient with both LCDD and AL amyloidosis, immunofluorescence studies became negative whereas Congo red staining of skin samples remained positive. In contrast, examination of the kidney showed light chain deposits in one patient with end-stage renal failure who achieved a complete immunological remission and had nephrectomy 3 years after high dose therapy. The kidney ablation was performed during renal transplantation, at a time when there was no evidence for recurrence either of monoclonal gammapathy (including no abnormal plasma cells on bone marrow smears) or of extrarenal deposits.

**Patients’ outcome**

Within a median follow-up of 51 months (14 to 129 months) since high dose therapy, two of the three patients with stage III and one patient with stage I multiple myeloma relapsed and were retreated by conventional chemotherapy 30, 40, and 24 months posttransplant, respectively. Otherwise, without any maintenance treatment, no patient developed a symptomatic multiple myeloma or modification of Ig levels.

No extrarenal manifestations related to Ig deposits occurred or recurred in any patient, including in those who did not achieve an immunologic response and in the patients in whom multiple myeloma relapsed. Similarly, nephrotic syndrome did not appear or re-appear in any patient. Renal function secondarily deteriorated in one patient with relapsing multiple myeloma who required hemodialysis 74 months posttransplant. Another patient, who had resistant stage I multiple myeloma, experienced secondary deterioration of renal function with a 75% increase in serum creatinine level (from 170 to 250 $\mu$mol/L) during the fourth year posttransplant.

During follow-up, only one patient died, 93 months posttransplant, because of progressive myeloma. At analysis, four patients required hemodialysis. The remaining patients, including one who underwent successful renal transplantation, had a serum creatinine level ranging between 100 and 250 $\mu$mol/L.

**DISCUSSION**

Until recently, very few patients with L(H)CDD have been treated by high dose therapy [8, 12]. Taking benefit of the growing experience of high dose therapy with stem cell support in patients with myeloma or AL amyloidosis, including those with renal failure (6, 7, 13, 14), we decided to use this therapeutic approach in all patients with L(H)CDD, provided they were under 65 years of age, had a relatively good performance status, and gave informed consent. Since 1990, all patients seen in our department and fulfilling these criteria were included in the present series.

In addition to the feasibility of high dose therapy with autologous blood stem cell support in patients with myeloma or AL amyloidosis, including those with renal failure (6, 7, 13, 14), we decided to use this therapeutic approach in all patients with L(H)CDD, provided they were under 65 years of age, had a relatively good performance status, and gave informed consent. Since 1990, all patients seen in our department and fulfilling these criteria were included in the present series.

In addition to the feasibility of high dose therapy with autologous blood stem cell support, this series documents its safety in patients with L(H)CDD. Indeed, although all patients presented with symptomatic renal and extrarenal manifestations typical of L(H)CDD [3, 15], including three with end-stage renal failure, three with symptomatic heart involvement, and one with both, no toxic death occurred either during ABSC mobilization or during high dose therapy and autotransplantation.
Moreover, no durable treatment-related deterioration of renal function occurred in any patient and the morbidity of the procedure was usually acceptable, particularly when stem cells were mobilized by G-CSF alone and when transplant cytoreduction used high dose melphalan alone. Of note, however, two patients with end-stage renal failure developed severe encephalopathy, which may be related to high dose melphalan [16]. In one of these, the dose of melphalan was 200 mg/m²; we no longer use this dosage in patients on hemodialysis even though melphalan pharmacokinetics has been reported to be normal in case of renal insufficiency [17]. In the other patient, who received 140 mg/m² of melphalan, encephalopathy was likely favored by central nervous system involvement, which is unusual in L(H)CDD but was observed by Randall et al in their princeps case [2].

This series also demonstrates that high dose therapy, effecting a high immunologic response rate with marked or complete suppression of the pathogenic MIg, often results in stabilization and even regression of L(H)C deposits with subsequent improvement in function of involved organs. This was particularly significant in the four patients with congestive heart failure who experienced impressive clinical and echocardiographic improvement and in the three patients with the nephrotic syndrome who achieved a major renal response. Importantly, histologic evidence for regression of L(H)C deposits was obtained in heart, liver, and skin. In addition, most responses were durable and, within a median follow-up of 50 months after high dose therapy, only one renal death and one patient death were observed, both when the underlying multiple myeloma had relapsed. These results compare favorably with those of conventional chemotherapy which rarely improves extrarenal manifestations due to L(H)C deposition and may benefit only some patients with moderate impairment of renal function [15, 18, 19]. Indeed, in 18 patients treated by conventional chemotherapy, Pozzi et al [18] observed worsening in renal function and development or extension of extrarenal symptoms in 11 and 7 patients, respectively. In the other main series of conventionally treated patients (N = 19), 5-year survival free of end-stage renal disease was 37% and 82% of the patients who initially had a serum creatinine concentration over 350 μmol/L progressed to end-stage renal disease despite therapy [19].

Recent reports of patients with AL amyloidosis treated by high dose therapy with stem cell support also document objective response with regression of amyloid deposits but underline the high morbidity and mortality of the treatment in these patients [11, 20, 21]. The incidence of toxic reactions, resulting in death rates up to 43% [20], far exceeds the rate of treatment-related
complications we have seen in high dose therapy for L(H)CDD. This difference may be due, at least in part, to the gastrointestinal tract toxicity of high dose therapy, which is much more marked in patients with AL amyloidosis than in those with L(H)CDD. In the former, amyloid infiltration of submucosal vessels in the bowel frequently causes gastrointestinal tract bleeding or perforation which may precipitate multiorgan failure [11], whereas gastrointestinal tract L(H)C deposits, if any, rarely produce complications.

Albeit involving a small number of patients, the present retrospective study argues in favor of high dose therapy with stem cell support in young patients with L(H)CDD. This treatment may improve renal and extrarenal manifestations due to L(H)C deposits and may prevent their progression without resulting in excessive morbidity or mortality, including in patients with severe organ failure. Moreover, as illustrated by one of our patients, those with end-stage renal disease may achieve immunologic and extrarenal remissions good enough to be subsequently proposed for renal transplantation.

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REFERENCES

16. Schum A, Dandridge J, Haydon P, Littlewood TJ: Encephalopa-
thy complicating high-dose melphalan. Bone Marrow Transplant 24:1141–1143, 1999
phalan with blood stem-cell support for the treatment of AL (amy-