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Phase II Trial of High-Dose Dexamethasone for Previously Treated Immunoglobulin Light-Chain Amyloidosis

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Immunoglobulin light-chain amyloidosis (AL) is a rare disorder characterized by production of a monoclonal light chain. This insoluble light chain, or a fragment thereof, deposits in tissues as amyloid and results in disruption of organ function and, ultimately, in death. Although melphalan and prednisone are beneficial in approximately 30% of patients with the disease, many patients fail to respond, and the median survival with this disease remains < 2 years. There is a need for new agents for those patients who fail to respond to melphalan-based chemotherapy. A study was undertaken of high-dose dexamethasone in the treatment of 19 patients with AL because of reports of its benefits in previously untreated patients with amyloidosis and its known activity in the management of multiple myeloma, which has many characteristics in common with AL. In this cohort, 3 of 19 patients showed an objective organ response of the disease. The median survival of the entire group was 11.2 months. We conclude that high-dose dexamethasone therapy is of occasional benefit in patients previously treated for amyloidosis. Combining dexamethasone with other therapies may increase the response rate. Am. J. Hematol. 61:115–119, 1999. © 1999 Wiley-Liss, Inc.

Key words: amyloid; amyloidosis; corticosteroid therapy; nephrotic syndrome

INTRODUCTION

Immunoglobulin light-chain amyloidosis (AL) is a plasma cell dyscrasia (formerly known as primary amyloidosis). Patients with AL produce a monoclonal light chain, or a fragment thereof, that can deposit as amyloid in organs and disrupt their function [1]. Purification of the light chain from the urine of humans with AL and its injection into mice reproduce this disease [2,3]. Although AL is a clonal disorder of light chains, the plasma cell component is not malignant, unless myeloma is present, showing neither progressive increase in the bone-marrow plasma cells over time, nor a tendency to develop lytic bone lesions as is seen in multiple myeloma [4]. In spite of the nonmalignant nature of amyloidosis, systemic chemotherapy with melphalan and prednisone has been used successfully in its treatment [5,6]. The mechanism is presumed to be the cytotoxic effect on the bone-marrow plasma cells, the source of the amyloidogenic light chain. Most patients (70%) show no demonstrable benefit from melphalan and prednisone, and the median survival of patients with this disease remains disappointing at approximately 1 to 2 years [7].

High-dose dexamethasone is clearly an effective agent in the management of multiple myeloma, with or without interferon [8]. It also has been used in the salvage therapy of patients with previously treated multiple myeloma, with a high response rate [9,10]. It appears to prolong the plateau phase in multiple myeloma [11]. Dhodapkar et al. [12] reported a high response rate and rapid response time to a combination of dexamethasone with interferon in patients with untreated amyloidosis. Based on this information, it was logical to consider high-dose dexamethasone in patients with biopsy-proven AL who had failed previous therapy.

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TABLE I. Characteristics of Patients

Characteristic	Patient findings		
	No. or range	Median	% Abnormal
Sex	14 M/5 F		
Age, yr	49–76	63	
Serum albumin, g/dL	0.93–3.45	2.41	21 (≤2 g/dL)
Creatinine, mg/dL	0.9–4.7	1.3	42 (>2 mg/dL)
Alkaline phosphatase, U/L	88–855	166	32 (2 × normal)
Serum M protein (n = 15), g/dL	0.1–3.42	0.1	20 (>1.5 g/dL)
Total protein, g/24 h	0.031–23.6	6.8	68 (>1 g/24 h)
Urine M protein (n = 18), g/24 h	0.003–2.81	0.24	17 (>1 g/24 h)
Marrow cIg+ plasma cell, %	1–52	7	
Echocardiogram			
Interventricular septal thickness, mm	10–20	14	47 (≥15 mm)
Ejection fraction, %	29–75	59	16 (<50%)

MATERIALS AND METHODS

Nineteen patients with biopsy-proven AL were entered consecutively into the study. Accrual of patients occurred from April 1996 through December 1997. No patient had multiple myeloma associated with AL. Fourteen of the 19 patients had been treated previously with melphalan and prednisone. One was treated with cladribine for an initial diagnosis of macroglobulinemia. Four had received low-dose corticosteroid treatment as empiric management for nephrotic syndrome before a diagnosis of amyloidosis had been established.

Patients were treated with high-dose dexamethasone in a dosage of 40 mg given orally on days 1–4, 9–12, and 17–20. These cycles were repeated at 4-week intervals for 3 consecutive cycles, and patients who had responded were placed on therapy at 40 mg on days 1–4 at 4-week intervals. Patients who failed to respond after three cycles were offered the opportunity to continue high-dose dexamethasone if there was no evidence of progression and if the toxicity related to therapy was not prohibitive. Patients were treated until death or until progression of their disease. No patient received concomitant therapy with interferon or any cytotoxic agents. No dose modifications were made for any degree of renal or hepatic dysfunction. No patient was excluded from the response or survival analysis.

To ensure that patients had the AL form of amyloidosis, all patients were required to have a demonstrable M protein in the serum or in the urine or a clonal population of plasma cells identifiable in their bone marrow. To participate, patients had to have a performance status (Eastern Cooperative Oncology Group, Statistical Center, Boston, MA) of 0 to 3, a creatinine concentration of < 5 mg/dL, and an alkaline phosphatase value < 4 times the institutional normal value. All patients underwent a baseline evaluation of the amyloidosis, including amyloid stains of the bone marrow and fat, immunofixation of serum and urine, and an echocardiogram to estimate the severity of cardiac amyloidosis. Patients receiving dexamethasone received a histamine H_2-receptor blocker (ranitidine) as prophylaxis against peptic ulceration and cotrimoxazole on a daily basis as prophylaxis for infection.

The response criteria required that patients with hepatic amyloidosis had to have a 50% reduction in their serum alkaline phosphatase concentration and complete normalization of hepatomegaly in the midclavicular line. In patients with nephrotic range proteinuria, 50% reduction of 24-hr urine protein was required in the absence of progression of the creatinine level. In patients with echocardiographic evidence of amyloid, the interventricular septal thickness had to decrease by 2 mm or the ejection fraction had to improve by 20 percentage points. Patients were evaluated after 3 cycles of treatment and every 6 months thereafter.

The study was approved by the Institutional Review Board of the Mayo Foundation, and all patients gave informed written consent before study entry in accordance with the Declaration of Helsinki.

RESULTS

The characteristics of the patients are given in Table I. As of December 1998, 12 of the 19 patients have died, and the median follow-up of the 7 survivors is 27 months (range, 10–29 months). The time between the diagnosis of amyloid and entry into this study ranged from 0 to 92 months, with a median of 7 months. Forty-seven percent of the patients entered the study within 6 months of their diagnosis. The syndrome distribution for patients in this study is given in Table II. Because patients had more than 1 amyloid-specific syndrome, the total number of syndromes exceeded the 19 patients in the study.

The diagnosis of amyloid generally can be established by noninvasive diagnostic tests such as the subcutaneous fat aspirate test (18 of 18) or amyloid staining of the bone-marrow biopsy specimen (16 of 19). Fifteen of the

TABLE II. Clinical Syndromes

Syndrome	Patients	
	Number	%
Renal (nephrotic range proteinuria)	12	63
Cardiac	12	63
Peripheral nerve	4	21
Hepatic	1	5
Autonomic nerve	3	16
Carpal tunnel	3	16
Tongue	2	11
Purpura	4	21
Malabsorption	3	16
Claudication	2	11
Pulmonary	1	5

TABLE III. Serum and Urine Immunoglobulin Findings*

Immunoglobulin	Patients	
	Serum	Urine
None	4	1
IgA-λ	1	
IgM-λ	2	
IgG-λ	2	1
Free λ only	10	17

*M protein in serum or urine in 19 of 19 patients.

patients had positive results of fat aspirate and bone-marrow tests, three patients had a positive fat aspirate with a negative bone-marrow result, and one patient did not have a fat aspirate test performed. There were seven renal biopsy specimens positive for amyloid and an additional three rectal biopsy specimens that demonstrated amyloid deposits. The production of M protein in our patients was modest (Table I). The median serum M protein value was only 0.1 g/dL because of the high prevalence of Bence Jones proteinemia (free light chains in serum rather than intact immunoglobulin molecules) seen in these patients (Table III). Only 5 of the 15 patients had an intact immunoglobulin molecule present in the serum, and only 3 of the 15 had a peak greater than 1.5 g/dL. Of the 18 patients with a urinary M protein, only 3 had a urinary M spike > 1 g/24 h.

Ten of the 12 deaths in our study occurred because of progressive amyloidosis. Seven patients died of either refractory congestive heart failure or sudden cardiac death due to an arrhythmia. One patient discontinued dialysis and died, and one patient died of renal failure. One patient died of combined renal and hepatic failure. One died of pulmonary embolus and infarction. One patient died of bacteremia that appeared unrelated to amyloidosis and may have been related to a diverticular perforation occurring during a 4-day cycle of high-dose dexamethasone; this may have been a treatment-related death. One other patient had to discontinue therapy because of disseminated herpes zoster and profound hypertriglyceridemia.

Ten of the patients had an M-protein response (Table IV). In 6 of the 10 patients, this represented the disappearance of a monoclonal λ light chain from the serum and urine. In all six, no measurable peak was visible and the disappearance was documented by immunofixation. In 2 of the patients, a monoclonal serum protein disappeared in its entirety, and in 2, a monoclonal serum protein decreased by > 50%. Only 1 of these 10 with an M-protein response fulfilled the criteria of response of an amyloid syndrome (patient 7).

Three of the 19 patients satisfied the criteria of response. One patient with renal amyloid previously treated with melphalan and prednisone had a > 50% reduction in urinary protein excretion, and the serum creatinine concentration decreased by 0.6 mg/dl. One patient previously treated with melphalan and prednisone who had cardiac amyloid and pulmonary infiltrates had complete resolution of the pulmonary infiltrates, and a third patient treated with low-dose steroids only had complete normalization of urinary protein loss and echocardiographic improvement of the amyloidosis. One patient at 3 months had a reduction of 24-h urine protein from 5.8 to 2.8 g/day, but during this same period, the serum creatinine concentration increased from 2.7 to 3.6 mg/dL and the patient was classified as a nonresponder. Three of the patients went on to hemodialysis. One is alive and has been on dialysis for 6 months, and 2 died at 7 and 11 months.

The actuarial median survival of the entire group is 11.2 months. This is not significantly different from other reported survivorships in treated patients with amyloidosis and does not appear to be an overall improvement; 1 of our 3 responders remains alive on therapy at 27 months and continues to do well.

DISCUSSION

High-dose dexamethasone is known to be effective in the management of multiple myeloma, demonstrating a 43% response rate in previously untreated patients [8] and a response rate of 57% when combined with interferon [9]. Dexamethasone is capable of inducing apoptosis of the plasma cell–one pathway is mediated by interleukin-6 and one is interleukin-6 independent [13].

Dhodapkar et al. [12] treated 9 patients who had amyloidosis with pulsed dexamethasone for 3 to 6 months followed by interferon (3-6 million units 3 times/week). Three patients also received maintenance doses of dexamethasone for the first year. Six of 7 patients with renal involvement fulfilled the criteria for response as defined in our study with a rapid response (median, 4 months). Marked improvement in organ function also was seen in patients with hepatic, neuropathic, and gastrointestinal

TABLE IV. Individual Patient Outcomes*

Patient	Age (yr/sex)	Serum M protein	Urine M protein	Organs involved	Response M protein	Response organ	Status, mo
1	56M	λ	λ	Heart, liver, CTS, purpura	Urine light chain disappeared	None	D, 11.6
2	49M	λ	None	Heart, peripheral & autonomic nerve	None	None	D, 9.6
3	74M	λ	λ	Kidney	Urine light chain disappeared	None	A, 27.5
4	63F	λ	λ	Kidney malabsorption	None	Urine protein loss 9.6 to 3.8 g/d	D, 17.6
5	62M	λ	λ	Heart, pulmonary, arthropathy, purpura, claudication	None	Pulmonary infiltrates resolved	D, 7.4
6	51M	None	λ	Kidney, heart	None	None	A, 28.8
7	63M	Gλ	Gλ	Heart	Serum M Protein 3.42 to 1.5 g/d	Urine protein loss 1.2 to 0.02 g/d	A, 27.4
8	70M	λ	λ	Heart	Serum M protein disappeared	None	A, 28.5
9	57M	None	λ	Kidney	Urine M protein disappeared	None	D, 24.7
10	76M	λ	λ	Kidney, peripheral nerve	None	None	D, 6.6
11	49F	λ	λ	Kidney, heart	Serum & urine M protein disappeared	None	D, 10.4
12	59M	Mλ	λ	Heart, kidney, peripheral & autonomic nerve	Urine M protein fell from 0.45 to 0.11 g/d	None	D, 10.4
13	58M	λ	λ	Heart, kidney, autonomic nerve	None	None	D, 4.4
14	59F	Aλ	λ	Kidney	Serum M protein disappeared	None	A, 18.2
15	71F	None	λ	Heart, kidney	None	None	D, 0.2
16	65M	Mλ	λ	Heart, peripheral nerve claudication, purpura, malabsorption	None	None	D, 0.9
17	65F	λ	λ	Heart, malabsorption	Urine M protein fell from 0.24 to 0.09 g/d	None	D, 5.0
18	66M	None	λ	Kidney	None	None	A, 10.0
19	67M	Gλ	λ	Kidney, purpura	Serum M protein fell from 1.28 to 0.5 g/d, urine M protein disappeared	Urine protein fell 50% but creatinine rose	A, 10.8

*A, alive; CTS, carpal tunnel syndrome; D, dead.

tract involvement. This promising data led us to initiate our protocol.

In this study, we elected not to combine interferon with dexamethasone. We previously studied interferon therapy in previously treated amyloidosis patients and found no objective responses with this agent [14]. Adam et al. [15,16] also found no therapeutic effect of interferon-α on AL. Moreover, Chidiac et al. [17], in treating amyloidosis with dexamethasone and interferon, reported symptomatic improvement in 9 of 9 patients, but all responses occurred while the patients were receiving high-dose dexamethasone before interferon, with the exception of 1 patient who had a decrease in proteinuria during the interferon phase. Moreover, interferon toxicity was graded as severe in 7 of 8 patients. Based on the toxicity reported and the lack of efficacy demonstrated in two prior reports, we elected not to use interferon in this study.

We cannot exclude the possibility that synergy between interferon and dexamethasone led to the results reported by Dhodapkar et al. [12], who noted renal responses in 6 of 7 patients treated. We saw renal responses in 1 of 12 patients. Perhaps prior therapy rendered our group resistant to the effects of dexamethasone.

In our cohort, only 3 of 19 patients responded when organ involvement was used as the end point. Because these patients previously had been treated with melphalan and prednisone and were not eligible for stem-cell transplant by virtue of prior alkylating agent chemotherapy or the extent of their cardiac involvement, the use of dexamethasone was a reasonable alternative, but only a minority responded. The median survival of < 1 year for a previously treated group is consistent with the poor survival reported for this disease (Fig. 1).

All nonrandomized studies of amyloidosis must be interpreted with caution because the mix of patients with the various amyloid syndromes can have a significant impact on survival. In our previous study [18] of vitamin

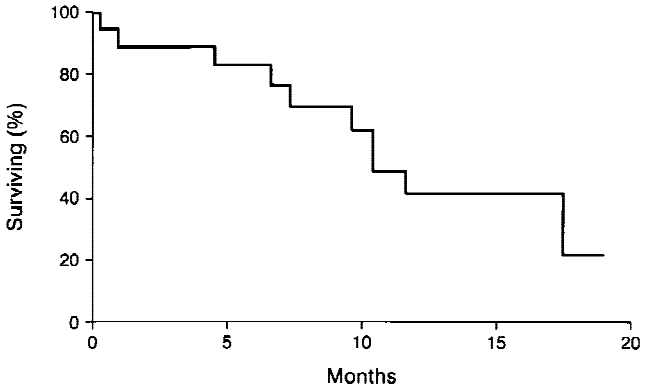

Fig. 1. Survival of 19 previously treated amyloidosis patients receiving high-dose dexamethasone therapy.

E in the treatment of amyloidosis, we found the median survival to be 19.4 months, suggesting that patients in the current cohort had more advanced disease. Moreover, a higher proportion of our patients had cardiac amyloidosis, which is known to have an adverse outcome. Only two patients in the study by Dhodapkar et al. [12] had cardiac amyloid, and neither of them responded.

We also noted that measurement of M protein responses, as is routinely done in myeloma, is not a suitable surrogate for assessing response in amyloidosis. Ten of our patients fulfilled the response criteria that normally would be applied in patients with multiple myeloma, yet only one fulfilled the response criteria for amyloid and organ response. Conversely, of the three responders, two did not fulfill the M protein criteria for multiple myeloma response, yet they had evidence of clinical regression of organ involvement. It was therefore misleading and should not be used as a response criteria in future studies of amyloidosis. We conclude that dexamethasone can provide benefit in a small proportion of previously treated patients with amyloidosis. Its use in amyloidosis can be considered as part of other therapy such as stem cell transplantation [19] or iododoxorubicin [20] or when other therapies are not available options. We currently use dexamethasone therapy in patients who fail melphalan and prednisone therapy who are not candidates for stem-cell transplantation.

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