Brief report

The combination of thalidomide and intermediate-dose dexamethasone is an effective but toxic treatment for patients with primary amyloidosis (AL)

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Based on the efficacy of thalidomide in multiple myeloma and on its synergy with dexamethasone on myeloma plasma cells, we evaluated the combination of thalidomide (100 mg/d, with 100-mg increments every 2 weeks, up to 400 mg) and dexamethasone (20 mg on days 1-4) every 21 days in 31 patients with primary amyloidosis (AL) whose disease was refractory to or had relapsed after first-line therapy. Eleven (35%) patients tolerated the 400 mg/d thalidomide dose. Overall, 15 (48%) patients achieved hematologic response, with 6 (19%) complete remissions and 8 (26%) organ responses. Median time to response was 3.6 months (range, 2.5-8.0 months). Treatment-related toxicity was frequent (65%), and symptomatic bradycardia was a common (26%) adverse reaction. The combination of thalidomide and dexamethasone is rapidly effective and may represent a valuable second-line treatment for AL. (Blood. 2005;105: 2949-2951)

Introduction

Primary amyloidosis (AL) is caused by light chains produced by a bone marrow plasma cell clone, usually of modest size.[1] Melphalan-based chemotherapy has been the mainstay of treatment.[2] Complete remissions are achievable in a substantial proportion of patients who are eligible for high-dose melphalan and autologous stem cell transplantation (ASCT).[3,4] Patients considered at poor risk are ineligible for ASCT, are in greatest need of rapidly effective therapy, and are usually treated with melphalan plus prednisone (MP); the response rate is approximately 30%.[5] However, time to response can be unbearably long (median, 11 months). Therefore, there is a need for drugs in addition to melphalan that can be used for treating AL. Previous studies from our group showed that high-dose dexamethasone (HD-Dex) alone achieved a 35% response rate in unselected AL patients[6] and, in association with melphalan, induced a 67% response rate in patients ineligible for ASCT.[7] A recent multicenter trial showed a 53% hematologic response rate with HD-Dex in AL.[8] Thalidomide is effective in refractory and relapsed multiple myeloma,[9,10] and, in vitro, it overcomes drug resistance of myeloma plasma cells synergistically with dexamethasone.[11] Thalidomide has been tested as a single agent in AL in 2 trials showing severe toxicity.[12,13]

In the present study, we evaluated the combination of thalidomide and intermediate-dose dexamethasone (T-Dex) in 31 patients with AL who did not respond to, or whose disease relapsed after, first-line therapy.

Study design

Thirty-one consecutive patients with symptomatic systemic AL with positive biopsy findings and evidence of plasma cell dyscrasia and who failed to respond to therapy (10 patients; 32%) or whose disease relapsed after first-line therapy (21; 68%) were entered in the study. Patients with symptomatic amyloid peripheral neuropathy were excluded. All patients gave written informed consent. Approval was obtained from the Policlinico San Matteo institutional review board.

First line therapy was MP (13 patients; 42%), ASCT (10 patients; 32%), or HD-Dex (8 patients; 26%). To detect possible adverse reactions to thalidomide (peripheral neuropathy, arrhythmia), neurologic evaluations (electromyography when indicated) and 24-hour Holter electrocardiography were repeated monthly in all patients.

Dexamethasone was administered cyclically (20 mg orally on days 1-4, every 21 days, for up to 9 cycles), whereas thalidomide was given continuously (100 mg orally every night, with 100 mg increments every 2 weeks if well tolerated, up to 400 mg). During dexamethasone administration, patients were given prophylactic omeprazole (20 mg/d), ciprofloxacin (250 mg bid), and itraconazole (100 mg/d). Patients did not receive prophylaxis against deep venous thrombosis.

Hematologic response to treatment was defined as a greater than 50% decrease in serum and urine monoclonal component (MC) evaluated by electrophoresis, or, if the MC was not quantifiable by electrophoresis, by the free light-chain test.[14] The functional improvement of the organs involved was assessed as previously reported by the Mayo Clinic Group.[5] Complete hematologic remission was defined as the disappearance of serum and urine MC at high-resolution immunofixation.[15] The response

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Table 1. Main clinical features of the 31 patients

	N (%)	Median (range)
Monoclonal protein		
κ	5 (16)	—
λ	24 (78)	—
Biclonal	2 (6)	—
Organ involvement		
Kidney	22 (71)	—
Heart	12 (38)	—
Liver	7 (23)	—
Skin	3 (10)	—
Gastrointestinal tract	3 (10)	—
Two or more organs involved	19 (61)	—
Postural hypotension	7 (23)	—
Urinary protein loss, g/24 h	—	4 (0-29)
Patients with urinary protein loss > 3 g/24 h	18 (58)	—
Serum creatinine concentration, mg/dL	—	1.1 (0.6-6.8)
Patients with serum creatinine concentration > 2 mg/dL	7 (23)	—
Interventricular septum (IVS) thickness, mm	—	14 (8-19)
Patients with interventricular septum (IVS) thickness > 15 mm	5 (16)	—
Ejection fraction, %	—	55 (35-72)
Patients with ejection fraction < 45%	6 (19)	—

— indicates not applicable.

was evaluated every 2 months and was established at the nadir of serum and urine monoclonal protein. Treatment was discontinued if the MC increased, if toxicity did not resolve after thalidomide dose reduction, or if complete hematologic remission, confirmed after 2 months, was achieved. After the ninth cycle of dexamethasone, only thalidomide administration was continued. Toxicity and adverse events were recorded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

Results and discussion

Thirty-one consecutive AL patients (18 males) were enrolled in the study between January 2001 and January 2003. Their median age was 62 years (range, 34-71 years). Ten patients had disease resistant to first-line therapy, and 21 had relapsed disease after an initial response. Median time from diagnosis to T-Dex initiation was 37 months (range, 10-97 months) for patients in relapse and 12 months (range, 6-23 months) for patients resistant to previous therapy. The main clinical features are reported in Table 1.

Overall, 15 (48%) patients achieved hematologic response, defined as complete remission in 6 (19%) patients, and 8 (26%) patients achieved functional improvement of the organs involved (50% or greater reduction of proteinuria in 6 cases, 50% or greater reduction of alkaline phosphatase, from 1392 to 680 U/L, reference less than 279 U/L, in 1 patient, and resolution of postural hypotension in 1 patient). Interestingly, 4 of the 8 patients initially treated with HD-Dex responded to T-Dex. Median time to hematologic response was 3.6 months (range, 2.5-8.0 months).

Eleven (35%) patients tolerated the 400 mg/d dose for at least 1 month. They received thalidomide for a median of 5.7 months (range, 4-14 months). The 20 patients who did not reach the target dose received thalidomide for a median time of 3 months (range, 0.5-13 months). Five (16%) patients did not exceed the initial 100 mg/d thalidomide dosage. In 9 (29%) patients, the dosage was escalated to 200 mg/d, and in 6 (19%) patients, it was escalated to 300 mg/d. The response rate was higher among patients receiving 400 mg/d thalidomide (hematologic response in 8 of 11 patients, complete remission in 3 patients, organ response in 4 patients). However, 35% of the 20 patients who did not tolerate the target dose responded to therapy (hematologic response in 7 patients, complete remission in 3 patients, organ response in 4 patients).

Overall, 20 (65%) patients experienced severe (grade 3 or higher) thalidomide-related toxicity (Table 2). No treatment-related deaths occurred within the first 3 months. Thalidomide median maximal tolerated dose was 300 mg/d (range, 100-400 mg/d).

Median follow-up of living patients is 32 months (range, 19-42 months). Nine patients died after a median follow-up of 9 months (range, 3.4-28.1 months) because of heart failure (7 patients), sudden death (1 patient), and renal failure (1 patient).

These data show that the combination of dexamethasone and thalidomide at full dosage (400 mg/d) in AL patients whose disease is refractory to or has relapsed after previous treatment provides good response rates (73% hematologic response, 27% complete remission, 36% organ improvement). However, in the present study, only 35% of patients could reach and tolerate the target dose because of the high incidence of adverse reactions to thalidomide. Nevertheless, we observed a substantial response rate (35% hematologic response with 15% complete remission and 20% involved organ improvement) in patients who received less than 400 mg/d thalidomide. Organ improvement was more frequent in patients with renal involvement, whereas cardiac amyloidosis did not improve. These results compare favorably with those observed in a previous study of thalidomide therapy alone in AL by the Boston group, who reported a significant reduction of Bence-Jones proteinuria only in 25% of 16 AL patients treated with thalidomide, with no complete remissions.[12] The Mayo Clinic reported that 2 of 12 AL patients enrolled in a trial of thalidomide alone had a 25% reduction in their serum monoclonal component.[13] In multiple myeloma, higher response rates (50%-75%) to thalidomide are

Table 2. Severe adverse reactions

Adverse events	Patients, N	%	Time from treatment initiation, mo	Maximum thalidomide dose, mg/d
Symptomatic bradycardia*	8	26	3.0 (0.2-6.9)‡	200 (100-400)‡
Sedation/fatigue	4	13	4.9 (0.5-7.2)‡	200 (100-400)‡
Constipation	2	7	0.7-2.8	100-200
Acute dyspnea†	2	7	1.9-5.1	300-400
Deep venous thrombosis	1	3	0.9	100
Skin lesions	1	3	0.5	100
Epilepsy	1	3	3.4	200
Renal failure	1	3	5.7	400

*No QT prolongation greater than the expected range because bradycardia was observed in any patient during 24-hour Holter ECG.
†Not pulmonary embolism.
‡Median value (range).

observed when the drug is combined with dexamethasone than when it is used as a single agent (response rate, 25%-40%).[16-22] Thus, it is possible that the higher response rate to T-Dex in AL, compared with that to thalidomide alone, was caused by a synergistic effect of thalidomide and dexamethasone, as was demonstrated in vitro on plasma cells.[11] Dexamethasone, alone or in combination with melphalan, is effective in AL.[6-8] The observation in the present study that 50% of patients treated with HD-Dex as first-line therapy responded to T-Dex indicates that combination therapy with thalidomide can overcome treatment failure with dexamethasone. The dose of dexamethasone used in the present study (20 mg on days 1-4, every 21 days) was lower than that reported in the previous study from our group[6] on HD-Dex (40 mg on days 1-4, every 21 days) and in the study by Dhodapkar et al[8] (dexamethasone schedule as in the VAD regimen for 3 cycles followed by maintenance dexamethasone, 40 mg on days 1-4, every month). Although lower doses of dexamethasone are probably less toxic and better tolerated, they might reduce the response rate. Moreover, the unavailability of the free light-chain test in previous studies on dexamethasone might have affected the response rate.

The observation of a high-incidence (65%) of thalidomide-related adverse reactions in patients with AL is in agreement with previous reports. Seldin et al[12] observed severe toxicity in 8 of 16 (50%) AL patients treated with thalidomide, and Dispenzieri et al[13] reported adverse reactions in 9 of 12 (75%) AL patients who received thalidomide, 6 of whom went off study because of the adverse effects. In the present cohort, symptomatic bradycardia emerged as a common (26%) adverse reaction to thalidomide in patients with AL. Bradycardia was reported in 1 of 16 patients by the Boston group[12] and in 1 of 12 patients by the Mayo Clinic Group.[13] A recent retrospective study performed on 96 myeloma patients treated with thalidomide showed a decrease in heart rate below 60 beats/min in 53% of patients and symptomatic bradycardia in 19% of patients,[23] which initially went unrecognized because studying the heart rate was not within the objectives of the original trial. In the present study, it is possible that performing monthly Holter electrocardiography (ECG) allowed us to recognize the correlation between bradycardia and the onset of symptoms such as dizziness, fatigue, and syncope. This close monitoring of heart rhythm might have played a role in reducing the occurrence of severe adverse effects because no treatment-related deaths were observed in the present study. Monthly Holter ECG might be of help in the follow-up of AL patients receiving thalidomide.

It was remarkable not to observe peripheral neuropathy in patients who might have had subclinical amyloid involvement of the peripheral nerves before the initiation of therapy. The absence of peripheral neuropathy in our series might have depended on the limited duration of treatment because of the earlier onset of other adverse reactions. Deep venous thrombosis was observed in only one patient, possibly because no other chemotherapy agents were administered concomitantly.[24,25]

In conclusion, T-Dex is effective in AL, but the low tolerability of thalidomide limits its applicability. This combination regimen may represent a viable option for second-line therapy, and, in view of its rapid action, it may be considered, perhaps in association with melphalan, for clinical trials for patients considered poor risk.

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