

# Oral Cyclic Melphalan and Dexamethasone for Patients With AL Amyloidosis

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## Abstract

**Purpose:** Aggressive treatment of amyloid light chain (AL) amyloidosis with high-dose intravenous melphalan followed by autologous stem cell transplantation (HDM/SCT) is effective in inducing hematologic remission and clinical improvement. However, only selected patients with AL amyloidosis are eligible for HDM/SCT because of amyloid-associated organ dysfunction. **Patients and Methods:** We report on 70 patients with AL amyloidosis treated with oral cyclic melphalan and dexamethasone. **Results:** Of 48 evaluable patients who survived and returned for follow-up assessment, 6 patients (13%) achieved a complete hematologic response and 12 patients (25%) a partial hematologic response. Responses were non-inferior for patients receiving weekly "low-dose" dexamethasone compared with those receiving 4 day pulses. Median survival for the 70 patients has not yet been reached with a median follow-up of 17 months. Nineteen patients (27%) received additional treatment leading to improvement in survival. **Conclusion:** Melphalan/dexamethasone can lead to hematologic responses and improvement in survival, particularly for those who can receive additional treatment for AL amyloidosis.

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## Introduction

Amyloid light chain (AL) amyloidosis is a plasma cell dyscrasia in which clonal immunoglobulin light chains misfold, forming amyloid fibrils that are deposited in tissues and vital organs, leading to organ dysfunction and failure.<sup>1</sup> Median survival of untreated patients is 10-14 months from the time of diagnosis and is marginally prolonged to 16-18 months with oral cyclic melphalan/prednisone regimen.<sup>2,3</sup> Moreover, this form of treatment rarely results in hematologic complete response (CR) or reversal of organ dysfunction.

High-dose intravenous melphalan and autologous stem cell transplantation (HDM/SCT) is effective in inducing both hematologic and clinical remissions in AL amyloidosis, and it appears to prolong survival substantially when hematologic remissions are achieved.<sup>4-6</sup> However, only selected patients with AL amyloidosis are eligible for HDM/SCT because of amyloid-associated

organ dysfunction.<sup>4</sup> Furthermore, treatment-related mortality for HDM/SCT because of amyloid-associated organ dysfunction remains a significant challenge<sup>7</sup> and failure to appropriately select and manage patients through the peri-transplantation period has led to mortality as high as 26% in multicenter trials.<sup>8</sup>

Recently, investigators have demonstrated the efficacy of treatment with oral melphalan and dexamethasone in inducing hematologic responses and improving survival for patients with AL amyloidosis who were not eligible for HDM/SCT.<sup>9</sup> In this report, 46 patients were treated with melphalan 0.22 mg/kg for 4 days and dexamethasone 40 mg for 4 days, and a complete hematologic response of 33% and a median overall survival (OS) of 5.1 years were observed. A subsequent randomized study from France showed no difference in response rate and survival between melphalan/dexamethasone and HDM/SCT.<sup>8</sup> In that report, melphalan/dexamethasone induced a complete hematologic response in 24% of 50 patients and the median OS was 4.7 years. Furthermore, the melphalan/dexamethasone treatment in patients with advanced cardiac amyloidosis led to complete hematologic response in 13% of patients and median survival was 10.5 months.<sup>10</sup>

To compare our experience with oral melphalan/dexamethasone in patients with AL amyloidosis, we have conducted a retrospective analysis of 70 patients with AL amyloidosis treated with oral melphalan and dexamethasone from 2004 to 2009 after initial evaluation in the Amyloid Treatment and Research Program at Boston

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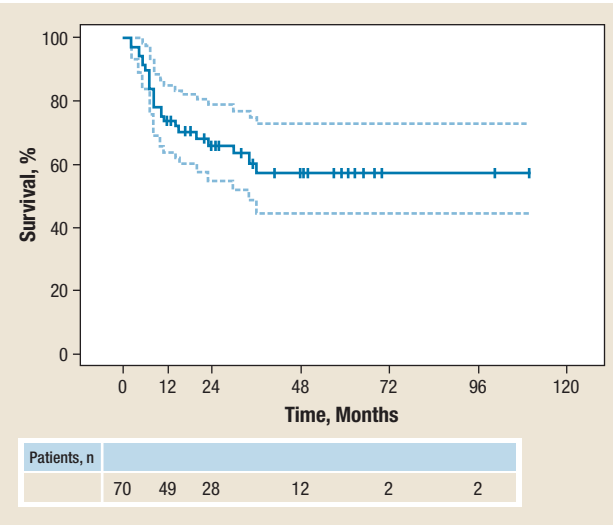


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**Figure 1** Kaplan-Meier Estimate of Overall Survival From the Time of Diagnosis, With 95% CIs, for All 70 Patients Treated With Oral Cyclic Melphalan/Dexamethasone (2004-2009)

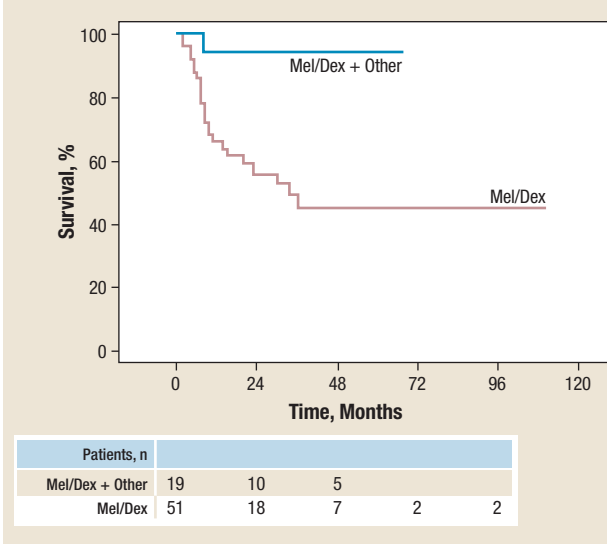


University Medical Center. Patients were treated by their primary hematologists, and follow-up data were gathered from patients, referring physicians, and on follow-up at our center.

## Patients and Methods

Patients with AL amyloidosis treated with oral cyclic melphalan and dexamethasone from 2004 to 2009 were studied with the approval of the Institutional Review Board of Boston University Medical Center. All patients had a histologic diagnosis of amyloidosis with evidence of a plasma cell dyscrasia and were not eligible for HDM/SCT treatment in clinical protocols at the time of initial evaluation or after going through stem cell mobilization and collection phase of treatment. Patients received oral melphalan at 0.22 mg/kg per day for 4 days and dexamethasone at 20-40 mg for 4 days (MD) and repeated every month for a total of 10 cycles or maximal hematologic response, whichever occurred sooner. The dose of dexamethasone was chosen as 20 mg or 40 mg depending on the age of the patient, cardiac status, and peripheral edema related to nephritic syndrome. In 2007, this regimen was modified based upon an Eastern Cooperative Oncology Group study demonstrating improved survival for patients with multiple myeloma treated with lenalidomide and low-dose (1 day a week) dexamethasone (Md).<sup>11</sup> Patients were followed for hematologic responses at 4-6 months after initiation of treatment and at the completion of treatment, and annually thereafter. Hematologic CRs following treatment required absence of monoclonal protein by immunofixation electrophoreses of serum and urine, normal serum free light chain levels, and ratio and normalization of bone marrow biopsy with < 5% plasma cells with no clonality. Hematologic partial response (PR) was defined as 50% reduction in serum M component if > 0.5 g/dL at baseline, or 50% reduction in urinary light chain if > 100 mg/day at baseline, or 50% reduction in involved serum free light chain concentration. Kaplan-Meier survival estimates were obtained for all patients from the time of diagnosis

**Figure 2** Kaplan-Meier Estimate of Overall Survival From the Time of Diagnosis for Patients Treated With Oral Cyclic Melphalan/Dexamethasone Alone and Treated With Oral Cyclic Melphalan/Dexamethasone Followed by Additional Treatment



using the log-rank test for comparisons. Analyses were 2-tailed using a  $P < .05$  significance level. Patients who survived through the end of the study period were considered censored observations.

## Results and Discussion

A total of 70 patients with AL amyloidosis received oral cyclic melphalan and dexamethasone from 2004 to 2009. Thirty patients were treated with the 4-day dexamethasone regimen (MD) and 40 patients received weekly dexamethasone (Md). Their median age was 65 years (range, 46-84 years); 50 (71%) were men. The median number of organ systems involved was 3 (range, 1-6 systems). Thirty-one patients (44%) had predominant cardiac involvement. Reasons for melphalan and dexamethasone selection rather than HDM/SCT included severe cardiac involvement ( $n = 25$ ), age > 75 years ( $n = 7$ ), patient choice ( $n = 6$ ), severe autonomic neuropathy ( $n = 6$ ), poor performance status ( $n = 11$ ), complications of stem cell mobilization and collection precluding HDM/SCT ( $n = 5$ ), and others ( $n = 10$ ).

Hematologic responses were assessed in 48 patients (69%) following treatment. Hematologic responses were not evaluable in 22 patients because of early death ( $n = 5$ ), toxicity of treatment leading to early termination of planned therapy ( $n = 6$ ) or failure to return for follow-up because of progression of disease or toxicity of treatment ( $n = 11$ ). Of the evaluable patients, 6 (13%) achieved a complete hematologic response and 12 (25%) achieved a partial hematologic response after a median of 4 cycles (range, 4-10 cycles). Hematologic responses occurred with MD and Md. The Md regimen did not appear to be inferior, as 5 of 6 CRs (83%) and 7 of 12 PRs (58%) occurred with Md ( $P = .6$ ).

Reasons for treatment termination included excessive myelosuppression ( $n = 7$ ), completion of planned treatment ( $n = 10$ ), progression of plasma cell dyscrasia or organ involvement ( $n = 19$ ),

nonhematologic toxicity (eg, steroid-induced myopathy, psychosis, or worsening heart failure [n = 8]), death while on treatment (n = 5), and unknown (n = 11). Nonhematologic toxicities were more commonly associated with MD rather than Md.

Median survival for all 70 patients from the time of diagnosis has not yet been reached at a median follow-up of 17 months. Kaplan-Meier estimates of survival with 95% confidence intervals (CIs) are shown in Figure 1. Overall 1-, 2-, and 3-year survival from the diagnosis is 73%, 66%, and 60%, respectively.

Nineteen of the 70 patients (27%), who did not achieve a hematologic response or who had a partial hematologic response, received additional treatment, including HDM/SCT (n = 3), orthotopic heart transplantation followed by HDM/SCT (n = 3), lenalidomide (n = 10) and/or bortezomib (n = 3). Median survival for the 19 patients treated with melphalan/dexamethasone followed by additional treatment has not been reached, whereas median survival is 34 months for the 51 patients treated with melphalan and dexamethasone alone (log-rank *P* value .0036; Figure 2).

In summary, oral cyclic melphalan and dexamethasone led to hematologic responses in 38% (CR, 13%, and PR, 25%) of patients with AL amyloidosis ineligible to undergo HDM/SCT. The hematologic CR rate in our study is lower than rates reported by Palladini et al<sup>9</sup> and Jaccard et al<sup>8</sup> (33% and 31%, respectively), however, similar to data reported by Lebovic et al.<sup>10</sup> This difference in CR rate could reflect the more stringent criteria for the definition of CR in our study, as the serum free light chain assay was not used to assess hematologic CR in the study by Palladini et al<sup>9</sup> and was used for less than half of patients in the study by Jaccard et al.<sup>8</sup> Selection bias, referral bias, or other differences between the patient groups might explain these differences. It does not appear to be due to the switch to weekly dexamethasone dosing, as in our patients, more responses occurred with this regimen (Md) than with the 4-day pulse regimen (MD).

This treatment regimen of oral melphalan/dexamethasone resulted in an OS of 60% at 3 years from the time of diagnosis, and median survival has not been reached with a median follow-up of 17 months. One third of patients received additional treatment with novel agents or HDM/SCT. This additional treatment may have contributed to improved survival in this group of patients that appeared medically fragile at initial evaluation, being ineligible for HDM/SCT. It is important to note that 3 patients in our study who were ineligible to receive HDM/SCT initially and received 3-4 cycles of oral melphalan/dexamethasone obtained a hematologic and clinical response, rendering them then eligible to undergo HDM/SCT. Improved survival could also be attributed to hematologic responses to melphalan/dexamethasone treatment regimen in addition to additional treatment with novel agents or HDM/SCT.

Mortality while on treatment with melphalan/dexamethasone occurred in 7% (n = 5 out of 70) of patients in our study, which is higher than was reported by Palladini et al.<sup>9</sup> This was related to disease progression and cardiac events in all 5 patients. In the Italian study, amiodarone was used in all patients, while we reserved amiodarone usage for patients documented to have an arrhythmia. It is possible that wider use of an antiarrhythmic may have prevented some cardiac events in the Italian study, and this is worth investigating further in a controlled fashion.

The limitations of our study are that it is a retrospective analysis of a “standard” treatment for patients not eligible for HDM/SCT and this treatment was performed by local hematologists. Therefore, the data collected on treatment toxicity were obtained from the patients or referring physicians’ office. There were 11 patients who did not return for follow-up and the data on their disease status or toxicity are not evaluable except for their survival. In retrospect, one wonders whether these patients were simply treatment failures and hence, did not return for follow-ups.

## Conclusion

The melphalan/dexamethasone regimen leads to hematologic responses and can be used as an alternative regimen for patients with AL amyloidosis ineligible for HDM/SCT, either as definitive therapy, or as a bridge to HDM/SCT or to regimens incorporating novel agents. The low-dose weekly dexamethasone schedule appears to be as effective as 4-day pulses, and in our experience was less toxic in terms of side effects of fluid retention and disturbance of sleep and mood.

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## Author Contributions

Vaishali Sanchorawala designed research, performed research, analyzed data, and wrote the manuscript. David C. Seldin designed research, performed research, analyzed data, and critically reviewed the manuscript. John L. Berk edited manuscript with critical review. J. Mark Sloan edited manuscript with critical review. Gheorghe Doros performed statistical analysis. Martha Skinner edited manuscript with critical review.

## Disclosures

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