

Low-dose continuous oral melphalan for the treatment of primary systemic (AL) amyloidosis

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Received 22 October 2001; accepted for publication 15 January 2002

Summary. Median survival of patients with AL amyloidosis with clinically significant cardiac involvement is 5 months when treated with cyclic melphalan and prednisone. We investigated a regimen of continuous oral melphalan as a single agent for patients with cardiac amyloidosis who were unable to tolerate prednisone or more aggressive chemotherapy. Thirty patients with amyloid cardiomyopathy were treated with continuous oral melphalan. Seven of 13

patients, evaluable after 3–4 months of treatment, achieved a partial haematological response and three achieved a complete haematological response; six patients have survived for > 1 year. This regimen appeared to be effective in inducing haematological responses in patients who received total doses of melphalan > 300 mg.

Keywords: AL amyloidosis, melphalan.

AL amyloidosis is caused by deposits of fibrillar immunoglobulin light chains derived from a clonal plasma cell dyscrasia. This form of amyloidosis leads to progressive multisystem organ failure and death associated with widespread amyloid fibril deposition. Cyclic oral melphalan and prednisone (MP) has been shown to extend the median survival of patients with this lethal disease marginally from ~13 months to ~17 months following diagnosis (Skinner *et al*, 1996; Kyle *et al*, 1997). More aggressive treatment of AL amyloidosis with high-dose intravenous melphalan followed by autologous stem cell transplant (HDM/SCT) has proven to be more effective in inducing haematological and clinical remissions, and in extending survival (Sanchorawala *et al*, 2001). However, many patients with advanced disease are unable to tolerate the toxicities of HDM/SCT, particularly those with cardiac involvement at the time of diagnosis. Similarly, cyclic oral MP may be complicated by glucocorticoid-induced fluid retention and worsening congestive heart failure in such patients. This group in particular has a poor prognosis, with a median survival of only 5 months from the time of diagnosis (Kyle & Gertz, 1995).

Continuous oral low-dose melphalan as a single drug regimen has been used previously in multiple myeloma. A randomized study comparing cyclic oral MP and continuous oral melphalan in newly diagnosed multiple myeloma concluded that response rates were better with MP than with continuous oral melphalan (45% vs 31%, $P < 0.05$). MP also achieved a longer median and 5-year survival in early stage I and II multiple myeloma than continuous oral melphalan (Ahre *et al*, 1983).

However, potential advantages of the low-dose continuous oral melphalan regimen for AL amyloidosis patients with severe cardiac involvement and short median survival include the omission of prednisone, which can exacerbate congestive heart failure and oedema, and increased melphalan dose intensity, which could possibly produce meaningful haematological responses more rapidly than standard cyclic MP. We therefore initiated a phase II study of low-dose continuous oral melphalan as treatment for patients with advanced AL amyloidosis and cardiac involvement who were ineligible for HDM/SCT.

PATIENTS AND METHODS

Thirty patients with AL amyloidosis were treated with low-dose continuous oral melphalan from August 1997 to May 2001, according to a protocol approved by the Institutional Review Board at Boston University Medical Center. The diagnosis of AL amyloidosis was established based on biopsy-proven evidence of amyloid deposits in tissue, in association with a bone marrow plasma cell dyscrasia

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and/or a monoclonal immunoglobulin light chain in the serum and/or urine detected by immunofixation electrophoresis. Of the 30 patients in this series, 27 (90%) had clinically significant cardiac involvement with moderate to severe congestive heart failure. The other three patients (10%) had predominant renal involvement requiring haemodialysis along with asymptomatic cardiac involvement by echocardiography and/or electrocardiography. Patient characteristics are shown in Table IA.

Low-dose continuous oral melphalan was given at 4 mg/d for 3 weeks, then withheld for 2 weeks, followed by resumption of melphalan treatment at 4 mg/d for 5 d/week. On this regimen, patients received 224 mg of melphalan in 12 weeks, compared with 112 mg in the same period of time for an average 70 kg patient receiving two cycles of cyclic MP using 0.2 mg/kg/d for 4 d (Skinner *et al.*, 1996). Treatment was withheld if white blood cell (WBC) or platelet counts declined below $3 \times 10^9/l$ or $50 \times 10^9/l$, respectively, but restarted once these counts had recovered. Treatment was initiated with the intention of administering a total dose of 600 mg over ~7–8 months. Patients were evaluated for both haematological response and clinical response after 3–4 months of treatment and again at the completion of treatment. A complete haematological response was defined as disappearance of the clonal plasma cell dyscrasia and monoclonal gammopathy by bone marrow immunohisto-

chemistry and by immunofixation electrophoresis (IFE) of serum and urine.

RESULTS

The median dose of melphalan received by the 30 treated patients was 202 mg (range 28–600). Seventeen patients (57%) died prior to an assessment of haematological response, which was scheduled to occur following 3–4 months of treatment. Of 13 patients assessed at 3–4 months and/or at completion of treatment, who received a minimum of 300 mg of melphalan, three (23%) achieved a complete haematological response (CR, i.e. disappearance of the associated plasma cell dyscrasia by bone marrow immunohistochemistry and monoclonal gammopathy by IFE of serum and urine), while seven (54%) achieved a partial response (PR). Three of 13 (23%) patients demonstrated progression of their plasma cell dyscrasia and of amyloid-related clinical disease. Thus, the response rate among evaluable patients was 77%, and 33% for the entire cohort of 30 patients in the study (10% achieving a CR and 23% achieving a PR).

The median survival of the study cohort of 30 patients was 5.7 months from the initiation of treatment. Six patients died of amyloid-related complications within 1 month of starting treatment. All deaths, after initiation of this treatment regimen, were caused by complications of end-stage amyloid cardiomyopathy (e.g. congestive heart failure, arrhythmias and thromboembolic events). However, six patients survived for > 1 year since the beginning of low-dose continuous oral melphalan with a median follow-up of 22 months (Fig 1). The three longest survivors in this series had achieved complete haematological response. Clinical features of long-term survivors and of those who achieved haematological responses did not differ noticeably from the clinical features of patients who did not respond (Table IB).

Myelosuppression was the only major treatment-related complication, but there were no cases of neutropenia-related infection. Seven of 30 patients (23%) required red cell and/or platelet transfusion support. The median number of units of packed red cell transfusion received was 2 (range 2–12) and of platelet transfusion was 5.5 (range 1–10). Twenty-four of 30 patients (80%) were hospitalized while receiving continuous oral melphalan for disease-related complications including worsening congestive heart failure, thoracentesis for pleural effusions, initiation of dialysis, syncope, stroke or gastrointestinal bleeding.

Table I.

A. Patient characteristics.

Characteristic	Finding
Age (years)	60 (range 45–90)
Male:female	1.2:1.0
Diagnosis to treatment (months)	2 (range 1–12)
≥ 2 organ involvement, <i>n</i> (%)	29 (97%)
Moderate to severe congestive heart failure, <i>n</i> (%)	27 (90%)
Arrhythmia, <i>n</i> (%)	9 (30%)
Embolic stroke, <i>n</i> (%)	5 (17%)
Pacemaker/defibrillator, <i>n</i> (%)	6 (20%)
Interventricular septal thickness in mm (median)	15 (range 9–22)
Performance status SWOG ≥ 2	23 (77%)

B. Clinical features of patients with haematological responses.

Clinical feature	Haematological response (<i>n</i> = 10)	No haematological response (<i>n</i> = 3)
Performance status SWOG < 2	3 (30%)	1 (33%)
≥ 2 organ involvement	9 (90%)	3 (100%)
Presence of serum M protein	8 (80%)	2 (66%)

SWOG, Southwest Oncology Group.

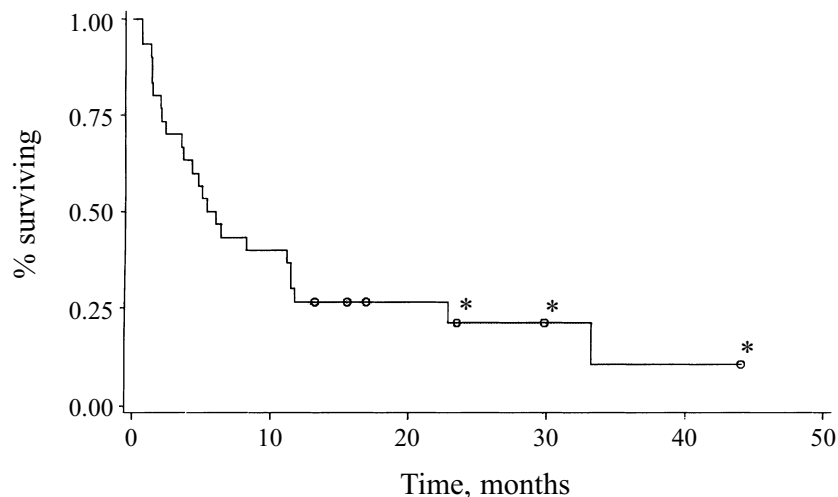


Fig 1. Kaplan-Meier survival curve demonstrating a median survival of 5.7 months from the initiation of treatment with low-dose continuous oral melphalan. Six out of 30 patients survived > 1 year; the three patients achieving a complete haematological response are indicated (*).

DISCUSSION

While melphalan given as a single agent (Waldenström, 1964) was the most widely used therapeutic regimen for multiple myeloma in Europe during the 1960s and early 1970s, comparative studies subsequently suggested that oral melphalan was more effective when combined with prednisone. However, in patients with AL amyloidosis and clinical cardiac involvement, prednisone may be poorly tolerated, exacerbating oedema and congestive heart failure. In such patients, we found that melphalan alone, given in a continuous regimen, was well tolerated, avoided prednisone toxicity and achieved a modest melphalan dose intensification. The present study focused specifically on patients with cardiac amyloidosis, in whom we wished to avoid the potential toxicities of corticosteroids. However, for patients without clinically significant cardiomyopathy and congestive heart failure, who are considered ineligible for HDM/SCT for other reasons, the addition of intermittent prednisone might further increase the efficacy of continuous oral melphalan, given as described in this report.

In a previous series of AL amyloidosis patients treated with cyclic oral MP, only 1 out of 33 patients (3%) with cardiac involvement survived for 2 years (Skinner *et al.*, 1996). Furthermore, cyclic oral MP leads to haematological complete responses in < 5% of patients. The low-dose continuous oral melphalan regimen leads to complete or partial haematological responses in the majority of patients who were able to receive a cumulative dose of melphalan of > 300 mg. Among this group of patients with an extremely poor life expectancy, three patients (10%) have lived for nearly 2 years.

There has been interest in achieving a modest degree of melphalan dose intensification, compared with standard-dose cyclic oral MP, for the treatment of myeloma through the use of single-dose intravenous infusions (e.g. 25–30 mg/m²), which do not require haematopoietic rescue with autologous stem cell transplant (Pertucci *et al.*, 1989; Back *et al.*, 1990). However, there is no published

experience with single, low-dose i.v. melphalan infusions in AL amyloidosis. Although this approach to achieving a degree of dose intensification may be more myelosuppressive than the continuous oral melphalan regimen described in the present report, it deserves study in patients with AL amyloidosis who are considered ineligible for more aggressive treatment with HDM/SCT.

Prolonged oral melphalan therapy has been associated with a dose-dependent risk of myelodysplasia (MDS) and/or secondary leukaemia. The risk of therapy-related MDS and leukaemia may be of limited importance in a population of patients with a short life expectancy. Nonetheless, in designing the present study, we considered it appropriate to limit the cumulative dose of melphalan administered by the low-dose continuous oral melphalan regimen in the event that complete haematological responses and prolonged survival were observed in some patients, as was the case. We chose 600 mg as a conservative cumulative dose limit in this regard based on the reported experience with cyclic oral melphalan. At the same time, we considered the 600 mg limit to be sufficient with regard to achieving the principal objectives of this study, i.e. to determine the frequency of haematological responses following treatment and to determine the tolerability of the regimen.

Based on these results, a multicentre phase III trial comparing MP with low-dose continuous oral melphalan for AL amyloidosis patients ineligible for HDM/SCT could be considered.

ACKNOWLEDGMENTS

This work was supported by grants from the Food and Drug Administration FD-R-001346 and from the Gerry Foundation. We gratefully acknowledge the numerous current and former colleagues in the Amyloid Treatment and Research Program, Clinical Trials Office and the Center for Cancer and Blood Disorders at Boston University Medical Center who assisted with the multidisciplinary evaluation and treatment of the patients with AL amyloidosis.

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