

Melphalan and dexamethasone for patients with multiple myeloma who are not candidates for autologous stem cell transplantation

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ABSTRACT

Background. Multiple myeloma is a disease for which a number of treatment options are available. The choice of therapy is often based on factors such as cost, ease of administration and faster response as the survival rates are similar with most of the regimens. We assessed the efficacy of a combination of melphalan and dexamethasone as first-line therapy in patients with multiple myeloma who were not candidates for autologous stem cell transplantation.

Methods. Thirty-four patients with multiple myeloma were included in the study. Patients received a maximum of 12 cycles of chemotherapy consisting of oral melphalan 8 mg/m² on days 1–4 and oral dexamethasone 40 mg on days 1–4 and days 9–12 every 4 weeks. Patients were assessed for response on the basis of M proteins and a bone marrow biopsy with touch preparation.

Results. The median follow up of surviving patients was 40 months. Nine patients (26.1%) had complete response/near complete response (5 had negative immunofixation) and 15 (44%) had partial response. The regimen was well tolerated and there were no therapy-related deaths. The 3-year overall and progression-free survival rates using the Kaplan–Meier method were 53% and 34%, respectively. The median duration of overall and progression-free survivals were 58 and 28 months, respectively.

Conclusion. The combination of melphalan and dexamethasone is safe and effective in patients with multiple myeloma who are not candidates for autologous stem cell transplantation.

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INTRODUCTION

Multiple myeloma accounts for about 1% of all cancer deaths.¹ For decades, the regimen of oral melphalan and prednisolone has remained the cornerstone of therapy for patients with multiple myeloma. With this regimen, the complete response (CR) rate is <10%, the overall response rate is 50%–60%, the median survival about 3 years, and the 5-year survival rate 25%.² Attempts have been made to improve upon these results by using combination

chemotherapy with multiple drugs resulting in overall response rates of 60%–70% and CR rates of 10%–15%, but no survival benefits.^{3–6} High dose chemotherapy followed by autologous stem cell transplantation (SCT) has a CR of 20%–40% with an overall response rate of 75%–90%.^{7–9} However, this is also not curative. Moreover, this treatment modality is associated with major side-effects and toxicity, is expensive and not feasible for all patients. The combination of melphalan and prednisolone thus remains the standard therapy for patients who are not candidates for autologous SCT owing to advanced age, poor performance status, pronounced renal failure, economic constraints or co-morbid conditions. The alternatives to melphalan and prednisolone are useful when a rapid reduction of tumour burden is required in case of renal failure or when the combination of melphalan and prednisolone is ineffective.

A combination of vincristine and doxorubicin administered as a continuous infusion along with intermittent high dose dexamethasone (VAD) provides a rapid response in newly diagnosed patients with multiple myeloma.^{11–14} Although it does not cause alkylating agent-mediated stem cell damage, its disadvantage is a 24% incidence of sepsis and thrombosis due to administration of drugs using a central venous catheter.^{11–12} Therefore, there is a need for treatment regimens that produce faster and better responses and are feasible for outpatient administration.

In the absence of a curative treatment for patients with multiple myeloma, strategies that enhance tumour reduction and survival duration are likely to be of clinical benefit. The activity of melphalan and dexamethasone as single agents for patients with multiple myeloma and *in vitro* evidence of their synergy provided the rationale for investigating this combination in newly diagnosed patients with multiple myeloma who were not candidates for SCT.

METHODS

Patient eligibility

This was a non-randomized, prospective, phase II, pilot study to evaluate the efficacy and toxicity of oral melphalan and dexamethasone in untreated patients with multiple myeloma who were not candidates for autologous SCT.

The diagnosis and staging for multiple myeloma were done according to the criteria defined by Durie and Salmon.¹⁵ Eligible patients were treatment-naïve, symptomatic (having a measurable monoclonal component), and not willing or not eligible to receive high dose chemotherapy and autologous SCT (age, medical contraindication or financial constraints). Only patients who gave informed consent for participation in the study and had a ECOG performance status <4 and a life expectancy >3 months were included.

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Patients who were asymptomatic, had non-secretory multiple myeloma, were eligible/willing to undergo autologous SCT, had uncontrolled diabetes mellitus or serum creatinine >3 mg/dl after adequate hydration were excluded. Patients with concurrent severe hepatic, cardiac or pulmonary disease were also excluded.

Clinical evaluation

Patient evaluation prior to treatment and at commencement of each cycle included haemoglobin, total and differential leukocyte counts, platelet counts, urea, creatinine, liver function tests, calcium, total proteins and serum albumin levels. In addition, serum and urine electrophoresis, immunofixation, bone marrow trephine biopsy and touch smear tests were done at baseline and after every 2 cycles.

Treatment regimen

Chemotherapy consisted of oral melphalan (8 mg/m²) on days 1–4 and oral dexamethasone (40 mg/day) on days 1–4 and days 9–12. The cycles were repeated every 28 days for a total of 12 cycles or until intolerance or disease progression was observed. In addition, all patients received trimethoprim–sulphamethoxazole 960 mg b.i.d. for prophylaxis against infections. Allopurinol was also given at a dose of 300 mg/day during the first 2 cycles.

Response and toxicity evaluation

Patients were assessed clinically prior to each course of chemotherapy. The following definitions were used:

Complete response (CR): Complete disappearance of myeloma paraprotein in the serum or urine with <5% plasma cells in a representative bone marrow sample.

Near CR (nCR): Absence of serum or urine M band which was not confirmed with immunofixation studies.

Partial response (PR): Reduction by >50% in serum paraprotein, (>90% reduction in urine M band) and bone marrow plasmacytosis with normalization of renal function and disappearance of symptoms.

Stable disease (SD): Stabilization of paraprotein with <25% deviation on a minimum of 2 occasions observed 4 weeks apart.

Disease progression (PD): >25% increase in paraprotein and/or bone marrow plasmacytosis.

Relapse: Reappearance of abnormality on serum or urine electrophoresis, bone marrow examination or skeletal survey.

Toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) Version 2 (www.fda.gov/cder/cancer/toxicityframe.htm).

Statistical analysis

Descriptive and comparative analysis of the results was done using non-parametric methods. Survival data were calculated using the Kaplan–Meier method.

RESULTS

Patient characteristics

Thirty-four patients with multiple myeloma (21 men; 61.8%) were included in the study from November 2000 to February 2004; 30 of these were evaluated for response. Their median age was 57 years (range 27–75 years). Two patients had stage IIA disease, 20 had stage IIIa disease (55.8%) and 12 had stage IIIB disease (35.3%) at the time of enrolment. Nineteen patients had IgG paraprotein, 2 had IgA paraprotein, while 12 had pure light chain disease (10 in the urine and 2 in the serum). In one patient M band was absent.

Response and survival

Analysis was done on an intent-to-treat basis. The median follow up of surviving patients was 40 months. Nine of 34 patients (26.1%) were in CR/nCR (5 had negative immunofixation and in the rest immunofixation could not be done) at a median of 4 cycles, 15 patients (44%) showed PR and 4 patients had SD (Table I). Two patients had PD, 1 died after the first cycle and 4 were lost to follow up without response assessment. At present, 3 patients are alive without any evidence of disease, 12 still have disease and 16 have died due to PD. The 3-year actuarial overall survival rate was 53% and the progression-free survival rate was 38%. The median overall and progression-free survival was 58 and 28 months, respectively (Figs 1 and 2).

Toxicity

There were no episodes of febrile neutropenia, opportunistic infections or peptic ulcers. None of the patients required hospitalization and treatment was completed in the outpatient setting. Dexamethasone was discontinued in 3 patients due to proximal myopathy after a median of 8 cycles. There were no treatment-related deaths.

DISCUSSION

High dose chemotherapy followed by autologous SCT significantly improves the response rate and survival of patients with multiple myeloma.^{7–9} However, a fair number of patients with multiple myeloma do not undergo SCT due to various reasons including the lack of adequate facilities and financial constraints. The regimen of melphalan and prednisolone has been the cornerstone of therapy for multiple myeloma for many years. It provides a 5-year survival rate of about 25% and an overall response rate of 50%–60%.² Combination chemotherapy such as the VAD regimen may be more effective than melphalan and prednisolone in inducing an objective and rapid response because of its activity against the bulk of plasma cells that proliferate slowly and are differentiated. On the other hand, alkylating agent-based therapy such as the combination of melphalan and prednisolone may be more active against rapidly dividing clonogenic cells, explaining the slower and perhaps more durable decline of myeloma paraprotein in patients who respond to melphalan. Although VAD therapy has a superior objective response, it has not been shown to prolong overall survival.^{3–6} In addition, VAD therapy has a higher rate of complications and it may not be the best option for patients who are not candidates for SCT. These patients are usually treated with melphalan and prednisolone.

The rationale for the combination of melphalan and dexamethasone to generate better and quicker responses has evolved through their use as single agents, *in vivo* and *in vitro* synergies^{20–23} and valid activity in combinational regimens such as VAD.^{16,17}

TABLE I. Response rates with a combination of melphalan and dexamethasone (n=34)

Assessment	Response		Disease		Not evaluable*
	Complete/near complete	Partial	Stable	Pro-gressive	
End of 4 cycles	6 (17.2)	14 (41.2)	7 (20.6)	3 (8.8)	4 (11.4)
Best response	9 (26.1)	15 (44)	4 (11.4)	2 (5.6)	4 (11.4)

*Lost to follow up before response assessment; however, survival data available Values in parentheses are percentages

Myeloma cells are known to express glucocorticoid receptors to which exogenous steroids bind, inhibiting mRNA expression of the growth factor interleukin-6 in these cells and inducing cytotoxicity.^{18,19}

High dose dexamethasone alone has proved to be one of the most active single agents for the induction of response in both refractory and untreated patients with multiple myeloma.¹¹⁻¹⁷ Moreover, it is frequently combined with other chemotherapeutic agents in treatment schedules and is a non-myelotoxic drug.

In vitro studies have demonstrated synergy between melphalan and dexamethasone. The effects of melphalan and dexamethasone on cell growth, cell cycle flow, cell loss and DNA cross-links have been studied in the myeloma cell line RPMI 8226.²⁰

Clinically, the combination of intermediate dose melphalan and dexamethasone has been used in newly diagnosed and relapsed patients with multiple myeloma.²¹⁻²³ In 62 high risk multiple myeloma patients, including relapsed and refractory cases, Petrucci *et al.*²¹ used intermediate dose intravenous melphalan (15–30 mg/m², day 1) and dexamethasone (40 mg day 1) followed by interferon for 6 courses. An overall response was seen in 61% of patients and 14.5% of patients had SD. Schey *et al.* used 25 mg/m² of melphalan as a 30-minute intravenous infusion with dexamethasone 40 mg daily for 4 days in 33 patients with *de novo* myeloma followed by maintenance with interferon; 82% had an overall response and 30% achieved CR at a median of 33 months with an acceptable toxicity profile.²²

Hernandez *et al.* randomized 201 elderly patients (>70 years old) to receive either melphalan and prednisolone or melphalan and dexamethasone for 12 cycles.²⁴ The overall response rate was similar in both arms. The proportion of CR was higher in the melphalan and dexamethasone arm (22.4% v. 9.1%, p<0.05). However, there was no significant difference in the event-free or overall survival rates at a median follow up of 54 months. One-fifth of the patients developed grade 3–4 haematological toxicity, the incidence of which was similar in both arms. Non-haematological toxicity was higher in the melphalan and dexamethasone arm and included infection, diabetes, neurological toxicity, cataract and necrosis of the head of the femur. The CR rates were marginally higher in our study but we did not encounter grade 3–4 haematological or non-haematological toxicity. The lower incidence of toxicity could be explained by the younger median age (55 years) of our patients.

We are aware that there are reports confirming the efficacy of thalidomide and dexamethasone as induction treatment before autologous SCT and also as first-line therapy.^{25,26} However, thalidomide needs to be taken daily and has major side-effects when taken along with dexamethasone for a long duration.²⁷⁻²⁹ In addition, the daily cost of thalidomide is an important consideration in our patients, who have limited resources.

In our study, all patients who responded had marked clinical benefits in terms of reduced pain, higher haemoglobin level, resolution of renal failure and reduced bone marrow plasmacytosis. The rapid responses observed after the administration of a median of 4 cycles and the high response rates (44% PR, 26% CR/nCR) demonstrate the advantages of this regimen as 32 of 34 patients (94%) had stage III disease and 12 patients (33%) had renal failure at presentation. The overall response rate of 70% seen in our study is superior to that reported with oral melphalan and prednisolone and is similar to that obtained with VAD infusion chemotherapy. Table II provides some of the reported response rates with a

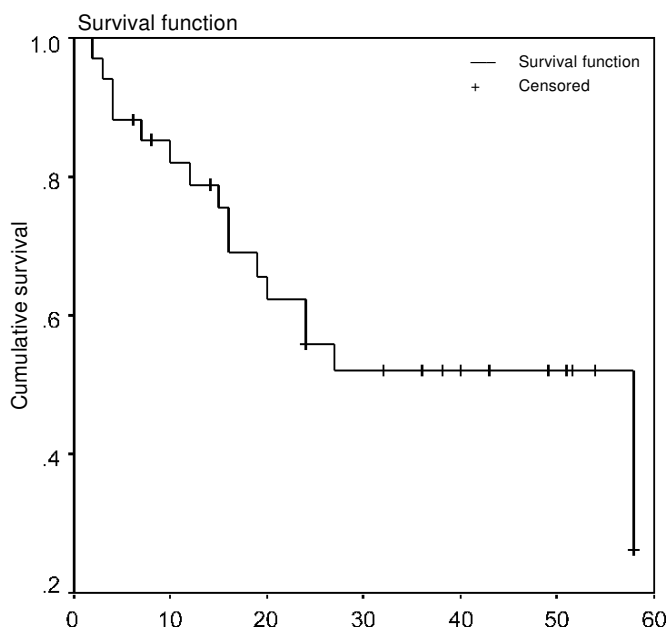


FIG 1. Overall survival (in months)

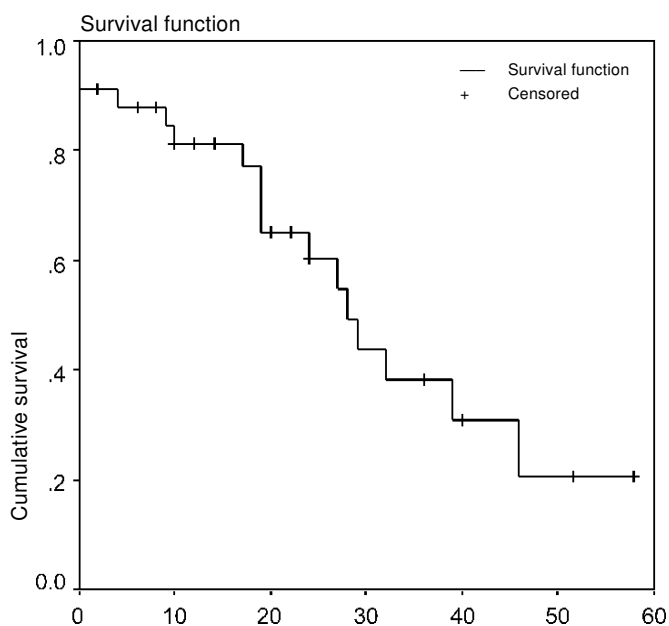


FIG 2. Progression-free survival (in months)

TABLE II. Reported response rates with a combination of melphalan–dexamethasone/prednisone

Study	n	Response	
		Complete/near complete (%)	Overall (%)
Myeloma Trialists [†] Collaborative Group ^{3*}	6633 (meta-analysis)	–	53.2
Petrucci <i>et al.</i> ^{21†‡}	62	–	61
Schey <i>et al.</i> ^{22†}	33	30	82
Hernández <i>et al.</i> ²⁴	101	22.4	64
Our study	34	26	70

* melphalan and prednisone † melphalan 25–30 mg/m² i.v. ‡ includes relapsed and refractory cases

combination of melphalan and dexamethasone compared with melphalan and prednisolone. Further, the delivery of this regimen on an outpatient basis and the acceptable side-effect profile makes it a viable alternative for patients who are not candidates for high dose chemotherapy and SCT.

Conclusion

Our study has shown response rates comparable to those observed with the VAD infusion regimen but better than those with melphalan and prednisolone. The safety of this combination in all the patients including those with renal failure has been documented. Hence, we feel that this combination is effective for patients who are not eligible/willing for high dose chemotherapy and autologous SCT, and should be evaluated further in randomized trials.

REFERENCES

- Jemal A, Murray T, Samuels A, Ghafoor A, Ward E, Thun MJ. Cancer statistics, 2003. *CA Cancer J Clin* 2003;**53**:5–26.
- Alexanian R, Haut A, Khan AU, Lane M, McKelvey EM, Migliore PJ, et al. Treatment for multiple myeloma. Combination chemotherapy with different melphalan dose regimens. *JAMA* 1969;**208**:1680–5.
- Myeloma Trialists' Collaborative Group. Combination chemotherapy versus melphalan plus prednisone as treatment for multiple myeloma: An overview of 6,633 patients from 27 randomized trials. *J Clin Oncol* 1998;**16**:3832–42.
- Gregory WM, Richards MA, Malpas JS. Combined chemotherapy versus melphalan and prednisolone for treatment of myelomatosis. *Lancet* 1992;**339**:1353–4.
- Hjorth M, Hellquist L, Holmberg E, Magnusson B, Rodjer S, Westin J. Initial treatment in multiple myeloma: No advantage of multidrug chemotherapy over melphalan–prednisone. The Myeloma Group of Western Sweden. *Br J Haematol* 1990;**74**:185–91.
- Cavo M, Benni M, Ronconi S, Fiacchini M, Gozzetti A, Zamagni E, et al.; Writing Committee of the 'Bologna 90' Clinical Trial. Melphalan–prednisone versus alternating combination VAD/MP or VND/MP as primary therapy for multiple myeloma: Final analysis of a randomized clinical study. *Haematologica* 2002;**87**:934–42.
- Attal M, Harousseau JL, Stoppa AM, Sotto JJ, Fuzibet JG, Rossi JF, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Français du Myelome. *N Engl J Med* 1996;**335**:91–7.
- Child JA, Morgan GJ, Davies FE, Owen RG, Bell SE, Hawkins K, et al. Medical Research Council Adult Leukaemia Working Party. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. *N Engl J Med* 2003;**348**:1875–83.
- Kovacs T, Delaly A. Intensive treatment strategies in multiple myeloma. *Semin Hematol* 1997;**34**:49–60.
- Rajkumar SV, Gertz MA, Kyle RA, Greipp PR. Current therapy for multiple myeloma. *Mayo Clin Proc* 2002;**77**:813–22.
- Alexanian R, Barlogie B, Tucker S. VAD-based regimens as primary treatment for multiple myeloma. *Am J Hematol* 1990;**33**:86–9.
- Segeren CM, Sonneveld P, van der Holt B, Baars JW, Biesma DH, Cornelissen JJ, et al. Vincristine, doxorubicin and dexamethasone (VAD) administered as rapid intravenous infusion for first-line treatment in untreated multiple myeloma. *Br J Haematol* 1999;**105**:127–30.
- Anderson H, Scarffe JH, Ranson M, Young R, Wieringa GS, Morgenstern GR, et al. VAD chemotherapy as remission induction for multiple myeloma. *Br J Cancer* 1995;**71**:326–30.
- Samson D, Gaminara E, Newland A, Van de Pette J, Kearney J, McCarthy D, et al. Infusion of vincristine and doxorubicin with oral dexamethasone as first-line therapy for multiple myeloma. *Lancet* 1989;**2**:882–5.
- Durie BG, Salmon SE. A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. *Cancer* 1975;**36**:842–54.
- Alexanian R, Barlogie B, Dixon D. High-dose glucocorticoid treatment of resistant myeloma. *Ann Intern Med* 1986;**105**:8–11.
- Alexanian R, Dimopoulos MA, Delasalle K, Barlogie B. Primary dexamethasone treatment of multiple myeloma. *Blood* 1992;**80**:887–90.
- Gomi M, Moriwaki K, Katagiri S, Kurata Y, Thompson EB. Glucocorticoid effects on myeloma cells in culture: Correlation of growth inhibition with induction of glucocorticoid receptor messenger RNA. *Cancer Res* 1990;**50**:1873–8.
- Ishikawa H, Tanaka H, Iwato K, Tanabe O, Asaoku H, Nobuyoshi M, et al. Effect of glucocorticoids on the biologic activities of myeloma cells: Inhibition of interleukin-1 beta osteoclast activating factor-induced bone resorption. *Blood* 1990;**75**:715–20.
- Fernberg JO, Lewensohn R, Skog S. Interaction of melphalan and dexamethasone in a human myeloma cell line. *Anticancer Drugs* 1991;**2**:565–70.
- Petrucci MT, La Verde G, Ribersani M, Avvisati G, Mandelli F. Intravenous melphalan and dexamethasone followed by lymphoblastoid alpha interferon in higher risk multiple myeloma patients. *Leuk Lymphoma* 2000;**39**:131–8.
- Schey SA, Kazmi M, Ireland R, Lakhani A. The use of intravenous intermediate dose melphalan and dexamethasone as induction treatment in the management of *de novo* multiple myeloma. *Eur J Haematol* 1998;**61**:306–10.
- Petrucci MT, Avvisati G, Tribalto M, Cantonetti M, Giovangrossi P, Mandelli F. Intermediate-dose (25 mg/m²) intravenous melphalan for patients with multiple myeloma in relapse or refractory to standard treatment. *Eur J Haematol* 1989;**42**:233–7.
- Hernández JM, García-Sanz R, Golvano E, Bladé J, Fernandez-Calvo J, Trujillo J, et al. Randomized comparison of dexamethasone combined with melphalan versus melphalan with prednisolone in the treatment of elderly patients with multiple myeloma. *Br J Haematol* 2004;**127**:159–64.
- Rajkumar SV, Hayman S, Gertz MA, Dispenzieri A, Lacy MQ, Greipp PR, et al. Combination therapy with thalidomide plus dexamethasone for newly diagnosed myeloma. *J Clin Oncol* 2002;**20**:4319–23.
- Cavo M, Zamagni E, Tosi P, Cellini C, Cangini D, Tacchetti P, et al. First-line therapy with thalidomide and dexamethasone in preparation for autologous stem cell transplantation for multiple myeloma. *Haematologica* 2004;**89**:826–31.
- Tosi P, Zamagni E, Cellini C, Plasmati R, Cangini D, Tacchetti P, et al. Neurological toxicity of long-term (>1 yr) thalidomide therapy in patients with multiple myeloma. *Eur J Haematol* 2005;**74**:212–16.
- Offidani M, Corvatta L, Marconi M, Malerba L, Mele A, Olivieri A, et al. Common and rare side-effects of low-dose thalidomide in multiple myeloma: Focus on the dose-minimizing peripheral neuropathy. *Eur J Haematol* 2004;**72**:403–9.
- Hall VC, El-Azhary RA, Bouwhuis S, Rajkumar SV. Dermatologic side effects of thalidomide in patients with multiple myeloma. *J Am Acad Dermatol* 2003;**48**:548–52.