Published in final edited form as:

Br J Haematol. 2010 March ; 148(6): 853–858. doi:10.1111/j.1365-2141.2009.08023.x.

Impact of Dexamethasone Responsiveness on Long Term Outcome in Patients with Newly Diagnosed Multiple Myeloma

Shirshendu Sinha, MBBS, S. Vincent Rajkumar, MD, Martha Q. Lacy, MD, Suzanne R. Hayman, MD, Francis K. Buadi, MD, Angela Dispenzieri, MD, David Dingli, MD, Ph.D., Robert A. Kyle, MD, Morie A. Gertz, MD, and Shaji Kumar, MD

Division of Hematology, Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA, 55905.

SUMMARY

Dexamethasone (Dex), alone or in combination, is commonly used for treating multiple myeloma. Dex as single agent for initial therapy of myeloma results in overall response rates of 50-60%. It is unclear whether steroid responsiveness reflects any biological characteristic that impacts long-term outcome. We studied a **cohort** of 182 patients with newly diagnosed myeloma seen between March 1998 and June 2007, initially treated with single-agent Dex for at least 4 weeks. The median age at diagnosis was 63 years (range, 39-81) and the median estimated survival was 55 months. At a median duration of therapy of 15 weeks, 91(50%) patients had a partial response or better, 80 (44%) had less than partial response and the remaining (6%) patients were not evaluable. The median overall survival from diagnosis for the responders was 75 months compared to 71 months for remaining patients, $p=0.6$. There was no correlation between baseline disease characteristics and Dex responsiveness. While overall survival was longer for the 130 (70%) patients who proceeded to an autologous stem cell transplant, no correlation was found between survival and Dex responsiveness among either group. Among this **cohort** of patients with myeloma, failure to respond to single agent steroid did not have an adverse impact on eventual outcome.

Keywords

Multiple Myeloma; dexamethasone; survival

INTRODUCTION

Multiple myeloma, a neoplasm of plasma cells, affects nearly 20,000 individuals each year in the United States(Jemal, *et al* 2008) and leads to considerable morbidity related to its clinical manifestations, such as destructive bone lesions, anemia, hypercalcemia, and/or renal insufficiency(Kyle, *et al* 2003, Kyle and Rajkumar 2004, Kyle and Rajkumar 2008). In the past decade, much improvement has been made in the area of myeloma therapy with the advent of novel agents, such as immunomodulatory drugs and proteasome inhibitors(Brenner, *et al* 2008, Kumar, *et al* 2008). Corticosteroids (Prednisone or Dexamethasone) have been an integral part of myeloma regimens for over five decades, and

Address correspondence to: Shaji Kumar, MD, Associate Professor of Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905; Phone (507) 266-0523; Fax: (507) 266-4972; kumar.shaji@mayo.edu..

Presented in part at American Society of Clinical Oncology Annual meeting, June-2009, Orlando, Florida, USA.

Financial Disclosures: SK: Research support from Celgene, Millennium, Novartis, Genzyme, Bayer; M.A.G: Research support from Genzyme, honoraria from Millenium and Celgene and serves on the Advisory Board of Amgen and Millenium.

continue to be used in conjunction with the novel agents(Alexanian, *et al* 1990, Alexanian, *et al* 1992, Alexanian, *et al* 1983, Lacy, *et al* 2006, Rajkumar, *et al* 2006, Richardson, *et al* 2005a). In fact, dexamethasone (Dex) was commonly employed for the initial induction therapy of myeloma prior to stem cell transplantation (SCT) before the advent of new therapies(Alexanian, *et al* 1986, Alexanian, *et al* 1992, Kumar, *et al* 2004a). The mechanisms of Dex's anti-myeloma activity are not fully understood(Sharma and Lichtenstein 2008). Dex reduces the monoclonal protein and increases therapeutic efficacy of various drug combinations used for the management of myeloma. The dose of steroids has been reduced in recent years as a result of a phase III trial demonstrating deleterious effect of high dose Dex on survival when used in combination with lenalidomide(Rajkumar, *et al* 2007). However, it continues to be used extensively in the setting of newly diagnosed as well as relapsed disease. The demonstration of improved outcome with novel agents(Brenner, *et al* 2008, Kumar, *et al* 2008) together with the adverse impact of high dose Dex when combined with novel agents like lenalidomide and the known toxicity from pulsed dose Dex, raises questions about the need for Dex in the setting of newly diagnosed disease. However, given the continued use of Dex in various combinations, such as Thalidomide/Dex, Lenalidomide/Dex, or Bortezomib/Dex, we investigated whether Dex sensitivity denotes any biological qualities of the tumor cell clone, which may translate into differences in long-term outcome. The results of using Dex as a single agent for initial therapy of newly diagnosed myeloma were reviewed and we investigated whether the responsiveness of Dex had any impact on the natural history of the disease.

PATIENTS AND METHODS

A total of 182 patients with newly diagnosed myeloma seen at Mayo Clinic between March 1998 and June 2007 within 30 days of their diagnosis, and initially treated with single agent Dex formed the study cohort. Patients had to have received at least 4 weeks of therapy with Dex to be included in the study. Patients in whom Dex was used in combination with another myeloma drug were excluded. All patients had provided written informed consent for use of their medical records. Approval from the Mayo Foundation Institutional Review Board was obtained in accordance with federal regulations and the Declaration of Helsinki.

Dex was typically administered in a pulse dose fashion (40mg/day) given on days 1-4,9-12 and 17-20 of a 28-day cycle. All patient received pneumocystis pneumonia prophylaxis with Bactrim DS, administered once daily. H2 blockers or proton pump inhibitors were used as clinically indicated. The M protein measurements were extracted from our prospectively maintained database or from medical records and the responses were re-assessed using the International Myeloma Working Group (IMWG) consensus response criteria.(Durie, *et al* 2006) The majority of patients (70%) proceeded to autologous SCT after a median of 4 cycles of therapy. These patients typically had stem cells collected with growth factor alone or in combination with cyclophosphamide and growth factor, which was followed by high dose melphalan given at 200 mg/m² with the dose reduced to 140 mg/m² among those with renal insufficiency or older patients.

The χ^2 and Fisher exact tests were used to compare differences between nominal variables and the Student's t-test or Kruskal Wallis test were used for continuous variables. Kaplan Meier analysis was used for analyzing overall survival (OS). Differences between survival curves were tested for statistical significance using the 2-tailed log-rank test. *P* values < 0.05 were considered significant. OS was defined as the time from transplantation or from the date of initial diagnosis of myeloma to the date of death or last follow-up, as the case may be.

RESULTS

A cohort of 182 patients with newly diagnosed myeloma, with a median age at diagnosis of 63 years (range; 39-81), 59% males, were included in the current analysis. The baseline characteristics and laboratory findings for the entire group are presented in Table 1. The estimated median OS for the entire group was 55 months. One hundred patients (55%) were alive at the time of the analysis with a median follow up of 50 months (range; 3 months to 9 years).

The median duration of Dex therapy was 15 weeks (range 4–193 weeks). Ninety-one patients (50%) obtained a partial response (PR) or better, including 10 patients (5%) who achieved a very good partial response (VGPR) or better. Eleven patients (6%) were not evaluable for a response. The remaining 80 patients (44%) had a response categorized as less than PR (minimal response or stable disease) or had progressive disease. Among the baseline disease characteristics, higher serum creatinine and higher urinary M protein were associated with a decreased likelihood of response to Dex (Table 1). In addition, the steroid non-responders had a higher proportion of patients classified as International Staging System stage III compared to the responders where the majority of the patients were in stage II. Among this cohort, 114 patients had cytogenetic results from around the time of diagnosis, of whom 9 patients had high-risk disease as defined by del 13 or hypodiploidy. Fluorescence *in situ* hybridization results were available from 60 patients at some time during the disease course. High risk disease was present in 14 patients, defined as presence of t (4;14), t (14;16) or 17p-.

The median OS from diagnosis was 75 months for the 91 responders as compared to 71 months for the remaining patients; $P = 0.6$ (Figure 1A). We also examined the outcome among the 140 patients (82%) who had a minimal response (MR) or better compared to the remaining patients. The median OS was 76 months among those with an MR or better compared to 43 months for the remaining; $P = 0.3$ (log rank test), 0.03 (Breslow-Gehan) (Figure 1 B)

One hundred and thirty patients (70%) proceeded to autologous SCT after a median of 4 months (range; 1-46 months) of Dex therapy. Eleven of these patients received a second transplant subsequently; 8 for subsequent relapsed disease, 3 had tandem transplants. There was no correlation between the degree of response to Dex and decision to proceed to transplant. Seventeen patients among this cohort received additional therapy prior to proceeding to transplant. While the median OS was longer among the group of patients who underwent SCT, among either group there were no survival differences between those with a PR or better to Dex compared to the remaining patients, $P = < 0.01$ (Figure 2A). Among the patients who underwent transplantation, the median progression-free survival (PFS) following transplant for those with less than a PR was 29 months compared to 32 months for those with a PR or better ($P=0.7$). Among this group of patients the post-transplant OS was similar among those with a pre-transplant response ($\geq$ PR) compared to the remainder, $P = 0.3$ (Figure 2B). Among the patients not receiving a transplant, the PFS for those with less than a PR with Dex was 3.4 months compared to 4.4 months for those with PR or better ($P=0.09$).

DISCUSSION

The advent of newer agents, such as thalidomide, lenalidomide and bortezomib, during the past decade has led to a shift in the initial therapy of myeloma. Prior to their introduction, patients eligible for high dose therapy were usually treated either with single agent Dex or other Dex-based regimens, such as VAD (Vincristine, Adriamycin, Dex) for 4 to 6 cycles

before undergoing SCT(Alexanian, *et al* 1990, Alexanian, *et al* 1992, Barlogie, *et al* 1986, Barlogie, *et al* 1984, Kumar, *et al* 2004a). Alkylator-based regimens were avoided in transplant-eligible patients given the concern for stem cell damage and impaired stem cell collection(Knudsen, *et al* 1999). The response with induction regimens such as Dex or VAD was around 50-60%, with very few patients achieving a complete response prior to SCT(Alexanian, *et al* 1992, Barlogie, *et al* 1984, Kumar, *et al* 2004a, Segeren, *et al* 1999). Dex plays a major role in the responses seen with combination regimens, such as VAD. However, Dex is a double-edged sword in the treatment of myeloma, because of the significant toxicities associated with its use.(Rajkumar 2008) Toxicities, including hyperglycaemia, psychological disorders, fluid retention, and sleep disturbances, limit its use as a single agent induction regimen. In the era of novel agents, Dex is still being used as part of different combinations, albeit at a lower dose. In a large phase III clinical trial comparing high or low (weekly) dose of Dex in combination with lenalidomide, use of reduced dose Dex actually resulted in improved survival despite lower response rates. Low dose Dex was better tolerated in patients with newly diagnosed myeloma.(Rajkumar, *et al* 2007)

Dex still continues to be used in combination with novel agents, such as lenalidomide and bortezomib, and is supported by results from *in vitro* studies as well as clinical trials demonstrating a synergistic role for Dex when combined with these agents.(Kumar, *et al* 2007, Lacy, *et al* 2006, Rajkumar, *et al* 2006, Rajkumar, *et al* 2007, Richardson, *et al* 2007a, Richardson, *et al* 2007b, Richardson, *et al* 2003a, Richardson, *et al* 2002, Richardson, *et al* 2005a) Given this scenario, we examined whether Dex responsiveness was a surrogate marker for biological characteristics that would favor better long-term outcomes. This would be a reasonable hypothesis, given that patients have a better response when Dex is used in combination with other active agents and this higher response rate and deeper responses may translate into improved survival.(Richardson, *et al* 2005b, Richardson, *et al* 2003b) We used a cohort of patients with newly diagnosed myeloma treated with single agent Dex as initial therapy in order to address this question specifically. We only included patients who had received at least 4 weeks of therapy, in order to provide an adequate therapeutic trial with Dex. We found that nearly half of the current patient cohort had a PR or better to Dex, consistent with previous reports (Alexanian, *et al* 1992, Kumar, *et al* 2004a). Interestingly, we found a lower response rate among those with decreased renal function and among those with higher amounts of M protein in the urine. This might reflect decreased tolerability and more frequent dose reduction in patients with renal dysfunction, but we were not able to examine this hypothesis. The lower response rate among those with higher urinary M protein may be due to *IGH* translocations in these patients.(Kumar, *et al* 2006) Clearly, Dex is an active agent in the treatment of myeloma with overall response rates similar to the novel agents when used alone. The current study did not find any relationship between long-term survival and initial responsiveness to Dex. While repeated use of Dex during the course of the disease may result in repeated responses, this does not appear to alter the natural history of the disease. This is consistent with the inability of Dex to induce durable responses, either in newly diagnosed or relapsed myeloma. In the recent phase III trials of newly diagnosed myeloma comparing novel agents with Dex, the median time to progression (TTP) was less than six months(Rajkumar, *et al* 2006, Rajkumar, *et al* 2008, Zonder, *et al* 2007). Even shorter TTP was seen with Dex in the setting of relapsed myeloma (Dimopoulos, *et al* 2007, Weber, *et al* 2007). In addition to being short lived the responses obtained from Dex are not typically as deep as demonstrated by very low rates of complete responses in these trials. We also saw a better OS among patients undergoing SCT, which is consistent with results of previous randomized trials.(Attal, *et al* 1996, Child, *et al* 2003). This is probably related to several factors, including the reasons that precluded the use of SCT, such as poor performance status, which by itself contributes to poorer outcome.

We conclude that among this group of patients with newly diagnosed myeloma treated with single agent Dex, steroid responsiveness did not have any long-term implications. It does not appear to predict response to SCT as has been shown before (Kumar *et al* 2004b). Responsiveness to steroids or lack thereof does not imply any additional risk to patients with myeloma and the results interpreted in the context of relatively unsustained nature of the steroid responses confirm the lack of any impact of Dex therapy on the natural history of the disease.

Acknowledgments

None

Supported in part by Hematologic Malignancies Program, CA 62242 and CA 10747603 (National Cancer Institute)

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Figure 1A.

Kaplan Meier curves demonstrating the overall survival from diagnosis, based on response to initial therapy with dexamethasone, partial response (PR) or better vs. < PR. The survival curves were compared using log rank test.

Figure 1B.

Kaplan Meier curves demonstrating the overall survival from diagnosis, based on response to initial therapy with dexamethasone, minimal response (MR) or better vs. < MR. The survival curves were compared using log rank test or Breslow Gehan Wilcoxon test.

Figure 2A.

Kaplan Meier curves demonstrating the overall survival from diagnosis, based on whether they received a stem cell transplant (SCT), further stratified by response, partial response (PR) or better vs. < PR. The survival curves were compared using log rank test.

Figure 2B.

Kaplan Meier curves demonstrating the overall survival from stem cell transplant based on response to initial therapy with dexamethasone, partial response (PR) or better vs. < PR. The survival curves were compared using log rank test.

Table 1

Baseline features at diagnosis

Characteristics	All patients (N=182)	Dex Responsive (N =91)	Dex refractory/ not evaluable (N =91)	P Value
<i>Variable</i>	<i>Median (range)</i>	<i>Median (range)</i>	<i>Median (range)</i>	
Age at diagnosis	63 (39-81)	62 (43-81)	64 (39-81)	0.3
Serum M protein (g/l)	29 (0.01-77)	32 (0.01-77)	27(0.01-69)	0.08
Serum Albumin (g/l)	37 (20-58)	36 (24-58)	37 (20-50)	0.85
Urine M spike (g/24 h)	0.49 (0.0-13.2)	0.29 (0.0-6.37)	0.865 (0.0-13.23)	0.02
Creatinine (μmol/L)	107 (62-937)	107 (62-663)	124 (71-1167)	0.003
Calcium (mmol/L)	2.4 (1.9-4.1)	2.4 (1.9-3.7)	2.4 (1.9-4.1)	0.38
BM plasma cell %	50.0 (1.0-93.0)	50.0 (2.0-90.0)	50.0 (1.0-93.0)	0.36
ISS Stage: 1 (%)	24.5	29.7	18.8	0.01
2 (%)	41.3	47.3	34.8	
3 (%)	34.3	22.9	46.4	
PCLI ≥1%, %	0.4 (0.0-18.0)	0.5 (0.0-18.0)	0.4 (0.0-7.0)	0.93
β ₂ microglobulin > 3.5 %	4.3 (0.36-77.5)	3.68 (0.36-77.5)	5.1 (1.28-34.0)	0.16

BM, bone marrow; ISS, International Staging System; PCLI, plasma cell labeling index