Reversibility of renal failure in newly diagnosed multiple myeloma patients treated with high dose dexamethasone-containing regimens and the impact of novel agents

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ABSTRACT

The impact of high dose dexamethasone containing regimens with or without the novel agents thalidomide and bortezomib on the reversal of renal failure (RF) was evaluated in 41 consecutive newly diagnosed patients with multiple myeloma (MM) treated in a single institution. RF was reversed in 73% of all patients within a median of 1.9 months. In patients treated with dexamethasone and novel agents (thalidomide and/or bortezomib) the reversibility rate was 80% within a median of 0.8 months. Severe RF and significant Bence Jones proteinuria were associated with a lower probability of RF reversal. Patients who responded to treatment achieved RF reversal more often than in those who did not (85% versus 56%, p=0.046). In conclusion, RF is reversible in the majority of newly diagnosed MM patients treated with high-dose dexamethasone containing regimens. The addition of novel agents induces a more rapid RF reversal.

Key words: dexamethasone, renal failure, myeloma, thalidomide, bortezomib.

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Renal failure is a common feature of multiple myeloma, providing a clue to the diagnosis of the disease and may pose a major management problem. Depending on the definition of renal impairment, this complication occurs in 20% to 40% of newly diagnosed MM patients.[1-3] The major causes of renal failure are the precipitation of monoclonal light chains in distal and collecting renal tubules and hypercalcemia. Dehydration, hyperuricemia and administration of analgesics and antibiotics with nephrotoxic potential also contribute to its development.[1-3] It has been reported that with supportive measures and antimyeloma treatment renal failure is reversible in 25 to 58% of patients.[1,2,4] In these series almost all patients were treated with alkylating agent-based regimens, usually with standard dose steroids.[1,2,4] In the late 80s, the introduction of high dose dexamethasone-based regimens in the treatment of MM resulted in both higher and more rapid responses compared to older low-intensity steroid regimens.[5-7] The impact of these high-dose dexamethasone-based regimens in the reversibility of RF in newly diagnosed patients has not been adequately reported. Furthermore, new agents such as thalidomide or bortezomib, either as a monotherapy or in combination with dexamethasone, have been very active in newly diagnosed MM patients.[8,9] There is some evidence that both thalidomide and bortezomib can be safely used in relapsed patients with renal impairment,[10-13] but their role in the management of newly diagnosed patients with myeloma and renal failure, and their impact in the reversibility of this complication, has not been studied.

The purpose of our study was to assess the reversibility rate of renal failure in newly diagnosed patients with myeloma who were treated in a single institution with high dose dexamethasone–based regimens, including patients who received thalidomide and/or bortezomib.

Design and Methods

Over the last decade, 41 consecutive patients with newly diagnosed myeloma and renal failure were treated in our institution with high dose dexamethasone-based regi-

mens. Renal failure was defined as a serum creatinine ≥2 mg/dL at the time of diagnosis. Besides antimyeloma treatment, all patients received intensive supportive care including intravenous hydration, alkalinization of urine, correction of hypercalcemia and discontinuation of all potential nephrotoxic agents. Renal dialysis was offered to all patients with an appropriate indication. All patients were eligible for assessment of reversibility of renal failure which was defined as a sustained decrease of serum creatinine to <1.5 mg/dL. Standard EBMT criteria[14] were used for assessment of response. In order to asses the impact of new agents in the reversibility of RF, patients were separated into two groups. Group A: 26 patients who received VAD, VAD-like regimens, melphalan plus high-dose dexamethasone or high-dose dexamethasone alone, and Group B: 15 patients who received high-dose dexamethasone with thalidomide and/or bortezomib. More specifically, 13 patients received dexamethasone 40 mg daily on days 1-4 and 9-12 with thalidomide 100 mg PO daily every 4 weeks. One patient received the same dose of dexamethasone with bortezomib 1.3 mg/m^2 IV on days 1,4,8,11 every 3 weeks and one patient received the latter regimen with added thalidomide 100 mg PO.

All analyses were performed using the SPSS statistical software (SPSS for Windows, version 13.1, SPSS Inc Chicago, IL, USA). Differences between groups were examined with a χ^2 test for categorical variables, whereas the t-test was used for continuous variables. Survival curves were produced with the Kaplan-Meier method. Multivariate analysis was performed by logistic regression for reversibility of RF. Throughout the analysis a level of 5% was used to denote statistical significance.

Results and Discussion

Patient characteristics are presented in Table 1. Either Bence Jones proteinuria or hypercalcemia were present in all patients. Most patients had features of advanced disease with stage 3 on the International Scoring System and with extensive marrow plasmacytosis. Almost one half of our patients presented with significant decline of their renal function (Table 1). In 10 patients (24%) renal replacement with dialysis was required to reverse life-threatening complications of renal failure. Plasmapheresis was not used in any patient. On an intention-to-treat basis, 53% of patients achieved at least a partial response to treatment, including 46% of patients in Group A and 64% of patients in Group B (p=0.272). The toxicity profile of the combination of new agents with dexamethasone was similar to that seen in patients without renal failure.

Reversal of renal failure was documented in 73% of all patients and the median time to reversal was 1.9 months (range 0.1 to 20 months). In all but 3 patients, renal failure reversed within 6 months. Eleven patients did not meet our criteria for renal failure reversal. However, in most of these patients there was some reduction of creatinine and four patients reached a serum creatinine level lower than 2 mg/dL. Thus, in 83% of patients, creatinine after treatment was <2 mg/dL. After treatment, only 2 of the 10 patients, who initially required dialysis remained on renal replacement therapy. Early death within two months from treatment initiation occurred in 3 patients (7.3%). Median survival of all patients from initiation of treatment was 23 months. Median survival was 23.5 months for those patients who achieved RF reversal and 21 months for those who did not (p=0.392).

Several variables were evaluated for their potential impact on renal failure reversal (Table 2). Patients who presented with light chain only myeloma or with Bence Jones proteinuria (≥2 gr/day or creatinine ≥4 mg/dL) had a lower probability of renal failure reversal. Furthermore, myeloma response to primary treatment was associated with higher probability of renal failure reversal (p=0.046). A multivariate analysis showed that there was a trend only for Bence Jones proteinuria ≥2 gr/day to be associated with a lower probability of renal failure reversal (p=0.075). There was no statistically significant difference in the rate of renal failure reversal among patients who were treated with or without new agents (Table 2). However, the median time to renal failure reversal was 2 months for patients of Group A and 0.8 months for patients of Group B (p=0.005) (Figure 1). Several other factors were evaluated for their

Table 1. Characteristics of 41 MM patients who presented with renal failure at initial diagnosis.

Gender	
Male	22 (54%)
Female	19 (46%)
Age Median / Range	65 (42-91)
Creatinine (mg/dL)1 Median / Range	3.4 (2-12.8)
Creatinine (mg/dL)1	
≥4	18 (44%)
<4	23 (56%)
Myeloma type	
IgG	18 (44%)
IgA	8 (19.5%)
Light Chain Only	15 (36.5%)
Calcium[2]	
≥11.5 mg/dL	10 (24%)
<11.5 mg/dL	31 (76%)
LDH	
>300 IU	7 (17%)
≤300 IU	34 (83%)
BJ protein	
≥2 gr/day	14 (34%)
<2 gr/day	27 (66%)
Anemia (Hgb < 10 gr/dL)	
Yes	32 (78%)
No	9 (22%)
BM PCs %	
>40	32 (80.5%)
≤40	9 (20.5%)
ISS	
I	0
II	8 (19%)
III	33 (81%

[1] to convert to mmol/L multiply by 88.4. [2]Corrected Calcium. To convert to mmol/L divide by 4.

Table 2. Factors affecting renal failure reversal.

	Reversal of RF	*p value univariate*	*p value multivariate*
Age			
≥75	9 (82%)		0.449
<75	21 (70%)		
Creatinine (mg/dL)			
≥4	9 (50%)	0.003	0.998
<4	21(91%)		
Light chain only MM			
Yes	8 (53%)	0.029	0.197
No	22 (85%)		
Calcium≥11.5 mg/dL			
Yes	6 (60%)	0.280	
No	24 (77%)		
BJ protein ≥2gr/day			
Yes	7 (50%)	0.004	0.076
No	22 (81%)		
Treatment Group A	18 (69%)	0.453	
Treatment Group B	12 (80%)		
Response to treatment			
Yes	17 (85%)	0.046	0.516
No	10 (55%)		

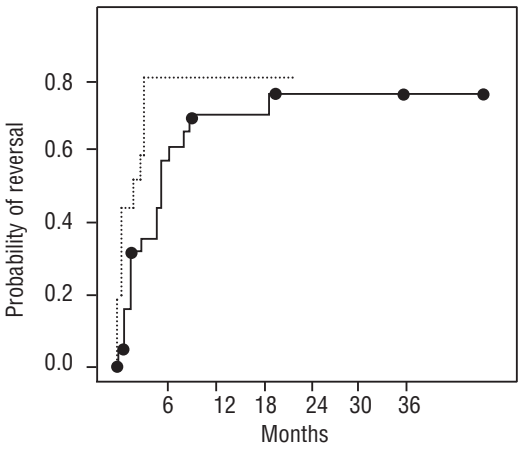

Figure 1. Probability of RF reversal according treatment: high dose dexamethasone plus new agents (thalidomide and/or bortezomib) (….) and high dose dexamethasone combinations without new agents (__).

impact on rapidity of renal failure reversal including myeloma type, degree of renal failure, hypercalcemia and amount of Bence Jones proteinuria. None of these factors were predictive.

Approximately 20% of patients with symptomatic multiple myeloma present with renal failure. This complication is associated with an increased probability of early death,[2,15] susceptibility to infections, problematic fluid management and drug dosing, prolonged hospitalization, increased cost and compromised patient's quality of life space.[1,2,4,15] Furthermore, patients requiring dialysis have additional complications when they are treated with high dose melphalan and autologous stem cell transplantation.[16,17] Restoration of renal function simplifies patient's' management and, in some analyses, is associated with improved survival.[2,4] Thus measures to reverse renal failure in as many patients as possible are highly desirable. Optimal management of acute renal failure in myeloma patients remains controversial.[1,2,4] However, two randomized trials failed to show any benefit with respect to renal failure reversibility for patients treated with plasma exchange added to standard chemotherapy.[18,19] To address these issues we evaluated a consecutive series of patients treated in a single institution during the last decade. All patients received maximum supportive care including dialysis if indicated. We used a cut-off of serum creatinine ≥2 mg/dL to define renal failure because this value may exclude patients with mild renal impairment that can only be easily corrected with hydration. Our study shows that, in patients treated with high dose dexamethasone-based regimens, renal failure is highly reversible, with 73% of patients restoring renal function within a median of 1.9 months from the initiation of treatment. This rate of reversal appears to be higher than those reported previously in series where patients were primarily treated with alkylating agent-based regimens.[1,2,4] High-dose dexamethasone-containing regimens induce a rapid reduction of light chain production[5-7] which is the main parameter related to the frequency and severity of renal failure in myeloma.[1-3] We also observed that the combination of high dose dexamethasone with thalidomide and/or bortezomib in patients with renal failure did not increase the frequency or severity of side effects and was associated with a more rapid rate of renal failure reversal. If these findings are confirmed by others, they may provide a sound basis to recommend these primary treatments to all patients with myeloma and renal failure regardless of their age and of their eligibility for high-dose therapy.

Previous analyses[1,2,4] had shown that large amounts of Bence Jones proteinuria, severe renal impairment and light chain only myeloma were associated with lower rates of renal failure reversal. In our study, creatinine >4 mg/dL, Bence Jones protein excretion of >2 gr/day and light chain only myeloma were associated with a significantly lower probability of renal failure reversal, although 50% of patients with creatinine ≥4 mg/dL, 50% of patients with high Bence Jones protein, and 53% of patients with light chain only myeloma, achieved creatinine <1.5 mg/dL. In contrast, only 8% of patients with severe renal failure treated with alkylating agents and standard steroid regimens reversed renal failure in an older study.[2] In another study, only 24% of patients with light chain only myeloma restored renal function.[1] In addition, 80% of our patients who initially required dialysis, became dialysis-independent compared with 0% to 60% of patients in other studies.[2,4,18,20] The rate of renal failure reversal among

those who responded to chemotherapy was higher (85% vs 55%), although in other analyses objective response was not associated with an increased probability of renal function improvemens.[1,4] However, about one half of our patients who do not meet EBMT response criteria recovered their renal function. We did not see a survival advantage in those patients who achieved renal failure reversal compared with those patients who did not. However, the number of our patients was relatively small. This observation is in accordance with some studies.[1] However, other studies indicate that restoration of renal function is associated with improved survival.[2,4] The fact that the median survival of our patients with non-reversible renal failure was similar to that of patients with reversible renal failure might be due to the severity of *persisting* renal failure, which was less severe than in the older series.[2] In fact, in the present series, 8 of the 10 patients requiring dialysis were dialysis-independent after treatment as opposed to the low rate of dialysis discontinuation in older series treated with alkylating agent-based regimens.[2]

To summarize, high-dose dexamethasone-based regimens result in high rates of renal function restoration in patients with newly diagnosed myeloma renal failure complications. These regimens were effective even in one-half of patients with poor-risk features for reversal such as extensive proteinuria, light chain only myeloma and significant renal impairment. Even patients presenting with acute severe renal insufficiency may experience an improvement in renal function and become dialysis-independent. Incorporating new biologic agents, such as thalidomide and/or bortezomib in the treatment regimens of these patients is safe, and results in a more rapid improvement of renal function.

Author Contributions

EK wrote the manuscript,was involved in the treatment of patients and collected data, AA was involved in the treatment of patients and revised the manuscript, DG analyzed the data, MR, CM, DP, IG, EP were involved in the treatment of the patients, AB analyzed the data and revised the manuscript, MAD treated the patients, designed the study and wrote the manuscript.

Conflict of Interest

The authors reported no potential conflicts of interest.

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