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Thalidomide-Dexamethasone as Induction Therapy before Autologous Stem Cell Transplantation in Patients with Newly Diagnosed Multiple Myeloma and Renal Insufficiency

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The aim of this study was to evaluate the efficacy and the toxicity of thalidomide-dexamethasone (Thal-Dex) as induction therapy before autologous peripheral blood stem cell (PBSC) transplantation in patients with newly diagnosed multiple myeloma (MM) with renal insufficiency. The study included 31 patients with a baseline creatinine clearance value ≤50 mL/min, 7 of whom required chronic hemodialysis. Patients received 4 months of Thal-Dex, followed by PBSC collection and subsequent transplantation. After induction, a partial response (PR) or greater was obtained in 23 patients (74%), including 8 (26%) who achieved a very good PR. Renal function improved more frequently in patients achieving a PR or greater (82%, vs 37% in patients achieving less than a PR; $P = .04$). Twenty-six patients underwent PBSC mobilization; in 17 of these patients (65%), $>4 \times 10^6$ $CD34^+$ cells/kg were collected. Double autologous transplantation was performed in 15 patients, and a single autologous transplantation was performed in 7 patients. After a median of 32 months of follow-up, median event-free survival was 30 months, and median survival was not determined. According to our data, Thal-Dex is effective and safe in patients with newly diagnosed MM and renal insufficiency. Given the relationship between recovery of renal function and response to induction treatment, more intensive Thal + bortezomib regimens could be explored to rescue higher numbers of patients.

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INTRODUCTION

Renal insufficiency occurs in approximately 20%-30% of patients with multiple myeloma (MM) at diagnosis and in >50% of patients with advanced disease [1,2]. Several previous studies have pointed out that despite their impaired renal function, a subset of these patients can safely receive high-dose therapy followed by autologous hematopoietic stem cell transplantation (HSCT) and can achieve response rates similar to those reported in patients with normal renal function [3-10]. Primary induction therapy is crucial, because prompt reduction of tumor burden combined with adequate supportive care can lead to improved renal function in a significant percentage of cases [11,12]. To achieve this important goal, rapidly effective, nonnephrotoxic induction regimens should be selected.

In most of the studies reported to date in patients with newly diagnosed MM with renal insufficiency, induction therapy involved either vincristine-doxorubicin-dexamethasone (VAD), eventually modified by replacing doxorubicin with another anthracycline, or high-dose-dexamethasone [4,8,11,12]. In recent years, many reports have drawn attention to the efficacy of thalidomide-dexamethasone (Thal-Dex) up-front in patients with newly diagnosed MM. Specifically, Thal-Dex has demonstrated a superior response rate compared with VAD in a case-matched paired analysis [13] and compared with high-dose dexamethasone in a multicentric randomized trial [14]. Our group has previously reported that Thal-Dex is active in patients with relapsed/refractory

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MM with renal insufficiency [15], with an acceptable toxicity profile. Pharmacokinetic studies have demonstrated that the kidneys apparently are not involved in Thal metabolism, because the drug undergoes spontaneous hydrolysis in plasma, and only a small amount is excreted unchanged in the urine [16]. Furthermore, no correlation between Thal clearance and renal function has been observed [17]. Although 2 small studies have shown an unexplained incidence of hyperkalemia in MM patients with renal insufficiency treated with Thal [18,19], we did not observe this side effect in our larger series of patients [15].

The aim of the present study was to investigate the role of Thal-Dex as initial therapy for patients with newly diagnosed MM and renal insufficiency who were candidates for subsequent autologous HSCT.

Table 1. Patient Characteristics

	Creatinine Clearance 30-50 mL/min	Creatinine Clearance <30 mL/min	Total
Number of patients	15	16	31
Males/females	13/2*	5/11*	18/13
Median age, years (range)	60 (46-70)	60 (45-70)	60 (45-70)
Isotype, n			
IgG	8	3	11
IgA	3	2	5
BJ	3**	10**	13
IgD	1	1	2
Light chain, n			
K	10	8	18
L	5	8	13
D&S stage III, n	9	10	19
ISS stage III, n	9	8	17

*$P = .006$.
**$P = .04$.

PATIENTS AND METHODS

Patients

Between May 2002 and February 2008, 31 consecutive patients (18 males, 13 females; median age, 60 years) with newly diagnosed MM and renal insufficiency provided informed consent to be enrolled in a clinical trial of Thal-Dex up-front in preparation for autologous HSCT. Baseline characteristics of the entire patient population are reported in Table 1. Renal insufficiency was defined as creatinine clearance ≤50 mL/minute according to the Cockcroft-Gault formula, confirmed by 2 different assays performed at least 72 hours apart after appropriate hydration therapy. Sixteen patients had a more severe renal impairment, as defined by creatinine clearance <30 mL/min, and 7 of these patients required chronic hemodialysis since diagnosis. Higher predominances of female patients and of patients with the Bence-Jones isotype were seen in the subgroup with a baseline creatinine clearance <30 mL/min.

Treatment Protocol

The study was an extension of the Bologna 2002 clinical trial [20]. According to the study design, patients received 4 monthly courses of combined oral Thal (100 mg/day for 2 weeks and 200 mg/day thereafter) and dexamethasone (40 mg/day on days 1-4, 9-12, and 17-20 on odd cycles and on days 1-4 on even cycles); fixed low-dose warfarin was administered as prophylaxis for deep venous thrombosis [21]. Peripheral blood stem cell (PBSC) collection was performed after priming with cyclophosphamide (Cy) 4 g/m^2 and granulocyte colony-stimulating factor (G-CSF) 5 μg/kg/day. G-CSF alone was used in patients with creatinine clearance remaining at <30 mL/min after induction therapy. The minimum threshold dose of CD34$^+$ cells collected in an attempt to safely perform a single or a double ASCT was 2 or 4 × 10^6 per kg of body weight, respectively. Autologous HSCT was subsequently carried out to support high-dose melphalan (HD-Mel) at 200 or 140 mg/m^2 depending on the creatinine clearance value (≥30 or <30 mL/min, respectively). Three months later, a second transplantation after preparation with HD-Mel was performed in patients with >4 × 10^6 CD34$^+$ cells/kg. Thal was administered continuously throughout the induction phase (4 months), then withheld to allow priming therapy with Cy + G-CSF or G-CSF alone. After PBSC harvest, Thal administration was resumed, and it was continued until completion of HSCT. The maximum duration of Thal therapy for patients undergoing double autologous HSCT was 8 months.

Renal function was monitored weekly during induction therapy, twice weekly during the transplantation procedure, and monthly thereafter.

Evaluation of Response

Criteria for defining a complete response (CR), a very good partial response (VGPR), a partial response (PR), or progressive disease (PD) were those reported by the International Myeloma Study Group [22].

Evaluation of Toxicity

Adverse events (AEs) were assessed and graded according to the National Cancer Institute's Common Toxicity Criteria, version 2.0.

RESULTS

Response to Induction Treatment

On an intention-to-treat basis, at least a PR was obtained in 23 patients (74%), including 3 (10%) who achieved a CR and 5 (16%) who achieved

Table 2. Response to Induction Therapy

	Creatinine Clearance 30-50 mL/min (n = 15)	Creatinine Clearance <30 mL/min (n = 16)	Total (n = 31)
PR, n (%)	11 (73%)	4 (25%)	15 (48%)
VGPR, n (%)	0 (0%)	5 (31%)	5 (16%)
CR, n (%)	2 (13%)	1 (6%)	3 (10%)

PR indicates partial response; VGPR, very good partial response; CR, complete response.

a VGPR (Table 2). Of the remaining 8 patients, 2 achieved a minor response, 2 were treatment-refractory, 2 exhibited disease progression, and 2 discontinued therapy after 1 month because of AE. No significant difference in the response rate to Thal-Dex, including VGPR or better response, was observed between patients with a baseline creatinine clearance >30 mL/min and those with a baseline creatinine clearance ≤30 mL/min (87% and 13% response rate vs 62.5% and 37.5%, respectively) (Table 2). No treatment-related deaths were recorded.

Renal Function

Recovery of normal renal function, defined as creatinine clearance >50 mL/min, was observed in 17 patients (55%). Six patients (19%) demonstrated improved creatinine clearance, with values ranging between 30 and 49 mL/min. In 9 patients, renal function remained severely impaired (creatinine clearance <30 mL/min) (Table 3). Normal renal function was achieved more frequently by patients with a lower degree of renal insufficiency at baseline (93%, vs 19% for those with creatinine clearance <30 mL/min; $P < .000$). Consistent with these data is the observation that all 9 patients who failed to recover or improve renal function had more severe renal impairment at baseline. Furthermore, an increased creatinine clearance value was significantly related to response to Thal-Dex: in fact, of the 23 patients achieving at least a PR, 19 (82.6%) had improved renal function, with 15 (65%) achieving a creatinine clearance value >50 mL/min. The corresponding value in those patients who failed to achieve a PR was only 37.5% ($P = .04$)

Table 3. Recovery of Renal Function

	Creatinine Clearance 30-50 mL/min (n = 15)	Creatinine Clearance <30 mL/min (n = 16)	Total (n = 31)
Creatinine clearance >50 mL/min, n (%)	14 (93%)*	3 (19%)*	17 (55%)
Creatinine clearance 30-50 mL/min, n (%)	1 (7%)	4 (25%)	5 (16%)
No improvement, n (%)	0 (0%)	9 (56%)	9 (29%)

*$P < .00$.

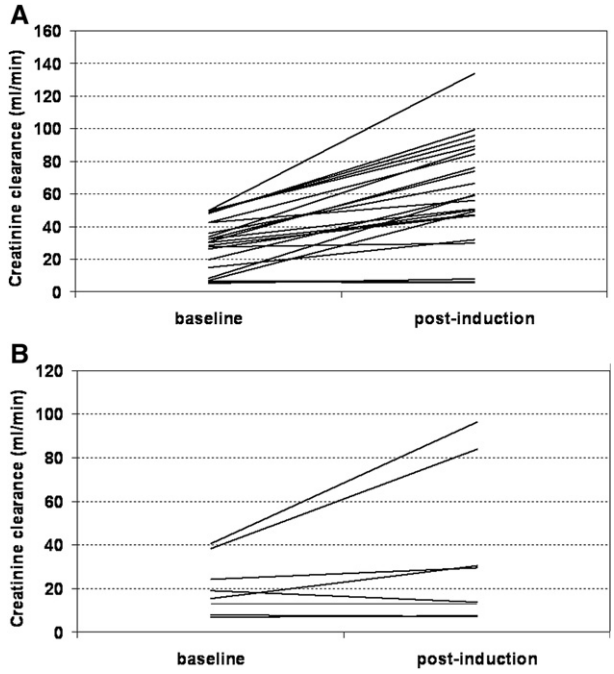

Figure 1. Renal function before and after induction therapy in patients achieving (A) or not achieving (B) at least a PR.

(Figure 1B), with only 25% of these patients attaining normal renal function. Two of 7 patients who were dependent on chronic hemodialysis became dialysis-independent; one patient who progressed on Thal-Dex experienced rapidly deteriorating renal function and underwent hemodialysis after 1 month of therapy.

AE

The toxic effects seen in this series of patients during induction therapy were comparable to those reported in patients with normal renal function [22]. Three patients (9.6%) developed deep venous thrombosis confirmed by Doppler ultrasonography; in one of these patients, induction therapy was discontinued, whereas the other 2 patients continued Thal while full anticoagulation therapy with low molecular weight heparin was instituted. Another patient discontinued treatment after 1 month because of an extensive skin rash, which resolved promptly after withdrawal of Thal. Additional side effects included grade 1 peripheral neuropathy (3 patients), constipation (2 patients), and lethargy (1 patient).

PBSC Mobilization and Collection

Five patients did not proceed to PBSC mobilization because of poor performance status (2 patients) or refractory/PD (3 patients, of whom 2 were subsequently salvaged with bortezomib-dexamethasone therapy). Of the 26 remaining patients, 4 failed to collect at least 2×10^6 $CD34^+$ cells/kg, 5 collected 2-4 $\times$ 10^6 $CD34^+$ cells/kg and thus were scheduled for single

Table 4. PBSC Collection and Transplantation Procedures

	Creatinine Clearance 30-50 mL/min (n = 15)	Creatinine Clearance <30 mL/min (n = 16)	Total (n = 31)
PBSC priming, n (%)	14 (93%)	12 (75%)	26 (84%)
Cyclophosphamide + G-CSF	14 (100%)	5 (42%)	19 (73%)
G-CSF alone	0 (0%)	7 (58%)	7 (27%)
PBSC collection, n (%)	14 (93%)*	8 (50%)*	22 (71%)
$CD34^+$ cells 2-4 $\times$ 10^6/kg	2 (14%)	3 (37.5%)	5 (23%)
$CD34^+$ cells >4 $\times$ 10^6/kg	12 (86%)	5 (62.5%)	17 (77%)
HSCT, n (%)	14 (93%)	8 (50%)	22 (71%)
Single	4 (29%)	3 (37.5%)	7 (32%)
Double	10 (71%)	5 (62.5%)	15 (68%)

PBSC indicates peripheral blood stem cell transplantation; G-CSF, granulocyte colony-stimulating factor; HSCT, hematopoietic stem cell transplantation.
*P = .025.

autologous HSCT, and 17 (55% of the entire population) collected >4 $\times$ 10^6 $CD34^+$ cells/kg, sufficient to support a double autologous HSCT (Table 4). PBSC collection was accomplished in a significantly lower percentage of patients presenting with greater impairment of renal function at baseline (50% vs 93%; P = .02). This could be ascribed both to a lower percentage of such patients proceeding to PBSC priming (75% vs 93%) and especially to a higher percentage of patients undergoing priming with G-CSF alone. In fact, of the 7 patients treated with G-CSF alone, 4 failed to collect at least 2 $\times$ 10^6 $CD34^+$ cells/kg, and 3 collected 2-4 $\times$ 10^6 $CD34^+$ cells/kg; conversely; 89% of the patients who were treated with Cy + G-CSF collected >4 $\times$ 10^6 $CD34^+$ cells/kg. No grade 3-4 extrahematologic toxicity was recorded in patients receiving cyclophosphamide + G-CSF as a PBSC priming regimen.

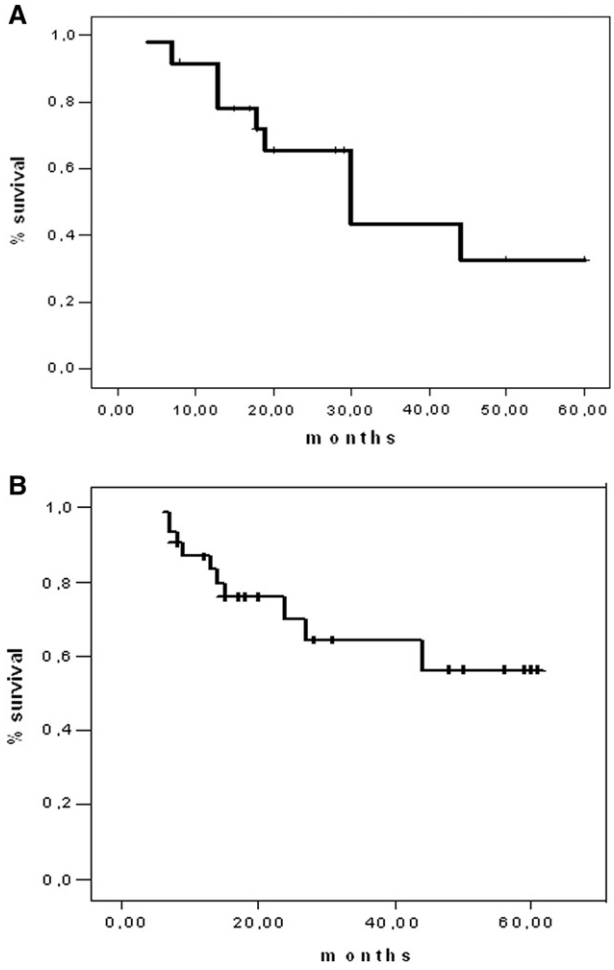

Figure 2. EFS (dotted line) and OS (solid line) of patients enrolled in the study. Data were analyzed on an intention-to-treat basis.

Transplantation Procedure and Transplantation-Related Toxicity

Of the 22 patients who successfully underwent PBSC collection, 15 received a double HSCT and 7 received a single HSCT because of either inadequate PBSC collection (5 patients) or delayed recovery of a good performance status after a first HSCT (2 patients) (Table 4). All of the patients demonstrated sustained engraftment, with 0.5 $\times$ 10^9 polymorphonuclear/liter and 20 $\times$ 10^9 platelets/liter after a median of 11 days and 13 days posttransplantation, respectively. While neutropenic, 6 patients experienced grade 3 fever with no microbiological evidence of bacterial/fungal infection. Grade III oral mucositis was observed in 3 patients. No transplantation-related deaths were recorded.

Final Response and Survival

On an intention-to treat basis, a VGPR or better was obtained in 13 patients (42%), 9 of whom (29%) achieved a CR. It is interesting to note that 11 of these 13 patients achieved normal renal function, compared with 3 of 18 patients who failed to achieve a VGPR (P = .00). The number of the patients enrolled in the trial was probably too low to allow us to detect a significant difference in response rate between patients receiving single HSCT (43% VGPR or better, with 14% CR) and those receiving double HSCT (66% VGPR or better, with 53% CR). At a median of 32 months of follow-up, overall median event-free survival (EFS) was 30 months, and median overall survival (OS) was not determined (Figure 2). Again, because of the small number of patients, we failed to observe a significant difference in median EFS (20 months vs 36 months) and OS (44 months vs not reached) between patents undergoing single and double autologous HSCT; nonetheless, EFS and OS curves did not differ significantly between patients with a baseline serum creatinine clearance of 30-50 mL/min and those with a baseline creatinine clearance of <30 mL/min (Figure 3).

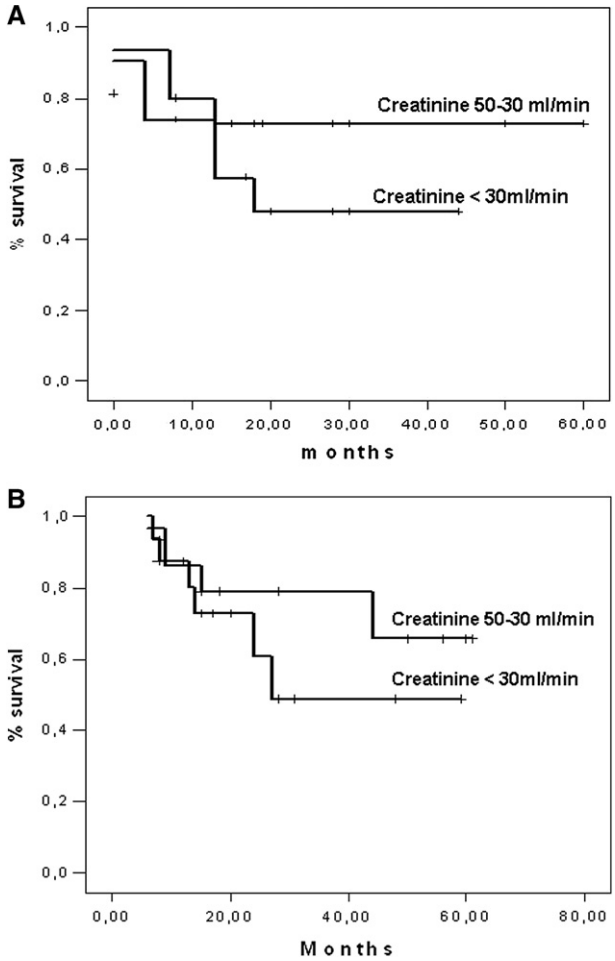

Figure 3. EFS (A) and OS (B) of patients presenting with a baseline creatinine clearance of 30-50 mL/min and <30 mL/min.

DISCUSSION

Thal-Dex has been demonstrated to be an effective and feasible induction treatment for patients with newly diagnosed MM [13,14]. In this present study, we investigated this drug combination as up-front therapy in a group of MM patients with renal insufficiency who were considered eligible for subsequent autologous HSCT. The rate of at least PR to Thal-Dex was comparable to that previously reported in patients with normal renal function [22] and probably superior to what can be achieved using other chemotherapeutic regimens [11,12], even though this statement has not been supported by prospective randomized trials. In addition, the rate of VGPR or better (26%) was similar to that reported by our group in the entire patient population enrolled in the Bologna 2002 clinical trial [20,23]. The overall safety profile of Thal-Dex in these patients is acceptable and comparable to that seen in patients with normal renal function.

A major problem that we faced when using this drug combination in this subset of patients was the feasibility of PBSC collection. Overall, only 58% of the initial patient population succeeded in collecting $>4 \times 10^6$ $CD34^+$ cells/kg, even though 22 of the 31 patients (71%) who were actually submitted to PBSC mobilization managed to collect at least 2×10^6 $CD34^+$ cells/kg. Although our data were obtained in a small patient population, this percentage is inferior to that reported with the use of Thal-based combinations in patients with normal renal function. A possible explanation for this finding could be that 7 patients (5 of whom failed to collect PBSCs) underwent priming with G-CSF alone, which likely is less effective than Cy + G-CSF in allowing more rapid stem cell collection and higher numbers of collected $CD34^+$ cells [24]. Some previous reports have noted that previous exposure to Thal might impair PBSC mobilization [25] or at least reduce $CD34^+$ cell yields [26], although not to an extent to make it impossible to perform a double autologous HSCT. Comparable results were seen with long-tern lenalidomide administration before PBSC collection without Cy priming in patients with normal renal function [27].

But, despite these problems with PBSC mobilization and collection (which need to be confirmed in a larger series of patients), neither engraftment nor toxicity was affected. After induction, 68% of the patients demonstrated improved renal function, with 55% achieving normal renal function. According to our data, reversal of renal insufficiency appears to be related to less-impaired renal function at the start of treatment, and in line with the results reported by Kastritis et al. [28] using either Thal or bortezomib in combination with Dex. Response to therapy seems to be a crucial factor in the reversal of renal insufficiency; patients achieving at least a PR have a greater probability of improving their renal function. Furthermore, a better quality of response (VGPR or better) is related to a higher probability of achieving a normal renal function at the end of treatment. Bearing this in mind, the treatment of patients with newly diagnosed MM and renal insufficiency possibly could be improved by increasing the speed and the rate of response; the addition of bortezomib to the original Thal-Dex combination could be explored for this purpose. Preliminary results of a randomized clinical trial of patients with newly diagnosed MM have demonstrated that Thal-Dex-bortezomib is more effective than Thal-Dex in terms of CR achievement [29], and that this advantage is maintained after autologous HSCT [30]. The possibility of worsening neuropathy with the combination of Thal and bortezomib should not be overlooked, however, even though preliminary data show that the incidence of grade ≥3 peripheral neuropathy does not exceed 9% [30]. Early studies have demonstrated that in patients with MM and renal failure, bortezomib-containing regimens are effective in terms of both reduction of tumor burden and

improvement of renal function [31,32]. Analyses of data from a large randomized trial conducted in patients with newly diagnosed MM [33,34] show that response rate and toxicity in the bortezomib-melphalan-prednisone arm (VMP) was not affected by renal failure; moreover, compared with the melphalan-prednisone arm, treatment with VMP resulted in a higher percentage of patients achieving normal renal function in a shorter period of time. Several studies [34-36] have pointed out that the reversal of renal failure after bortezomib-containing regimens is related to the response to therapy, and also that these regimens warrant rapid responses, which might be crucial to increasing the likelihood of reversing renal insufficiency. Bortezomib seems to act specifically on the pathogenesis of myeloma-related renal insufficiency. Inhibition of nuclear factor kappa light-chain enhancer of activated B cells could potentially prevent the cytokine-mediated inflammatory damage to the kidney interstitium seen in MM [37-39], as well as the mesangial alterations that can be detected in light-chain deposition disease [40,41]. These findings, together with our data, suggest that Thal-bortezomib combination therapy might be useful as initial therapy in patients with MM and renal insufficiency.

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