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Thalidomide plus dexamethasone as a maintenance therapy after autologous hematopoietic stem cell transplantation improves progression-free survival in multiple myeloma

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Despite the good response of stem cell transplant (SCT) in the treatment of multiple myeloma (MM), most patients relapse or do not achieve complete remission, suggesting that additional treatment is needed. We assessed the impact of thalidomide in maintenance after SCT in untreated patients with MM. A hundred and eight patients (<70 years old) were randomized to receive maintenance with dexamethasone (arm A; *n* = 52) or dexamethasone with thalidomide (arm B; *n* = 56; 200 mg daily) for 12 months or until disease progression. After a median follow-up of 27 months, an intention to treat analysis showed a 2-year progression-free survival (PFS) of 30% in arm A (95% CI 22–38) and 64% in arm B (95% CI 57–71; *P* = 0.002), with median PFS of 19 months and 36 months, respectively. In patients who did not achieve at least a very good partial response, the PFS at 2 years was significantly higher when in use of thalidomide (19 vs. 59%; *P* = 0.002). Overall survival at 2 years was not significantly improved (70 vs. 85% in arm A and arm B, respectively; *P* = 0.27). The addition of thalidomide to dexamethasone as maintenance improved the PFS mainly in patients who did not respond to treatment after SCT. Am. J. Hematol. 87:948–952, 2012. © **2012 Wiley Periodicals, Inc.**

Introduction

High-dose therapy supported by autologous hematopoietic stem cell transplantation (ASCT) has become the mainstay for the treatment of multiple myeloma (MM) in patients up to 65 years of age. Compared with conventional chemotherapy, ASCT has been shown to improve response rates and prolong progression-free survival (PFS), and overall survival (OS) [1,2]. Unfortunately, most patients relapse after ASCT, suggesting that additional treatment is needed to prolong PFS. Maintenance and/or consolidation therapies have been shown to improve outcomes in patients receiving ASCT-based treatment and have a significant impact on both OS and PFS [3,4].

Thalidomide, an immunomodulatory agent with antiangiogenic properties, was first introduced as a treatment for MM in 1999 [5]. The impressive results and acceptable toxicity observed in patients with advanced relapses and refractory disease qualified thalidomide as a potential candidate for maintenance therapy after ASCT. The use of thalidomide alone or in association with corticosteroids after ASCT improved overall response rates, event-free survival, and OS in two large, randomized clinical trials [3,4]. Based on these data, the Brazilian MM Study Group designed a clinical trial to evaluate the impact of thalidomide in maintenance after ASCT.

Methods

This multicenter, prospective, and randomized trial was conducted in four centers from October 2003 to July 2008. The protocol was approved by the ethics committee of each center, and all patients signed an informed consent form before beginning any study procedure. This study was registered at http://clincaltrials.gov as NCT01296503. Randomization was performed at a central location using sealed envelopes and computer-generated numbers.

The following were the inclusion criteria used in this study: symptomatic MM in accordance with the International Myeloma Working Group criteria, [6] age 18–70 years, ECOG performance status of 0–2, and normal hepatic function (defined as serum bilirubin <3 mg/dL and AST and ALT <4 times normal). Exclusion criteria included evidence of disease progression after ASCT (before randomization), cardiac dysfunction (systolic ejection fraction <50%), chronic respiratory disease (carbon monoxide diffusion <50% of normal), or any comorbidity likely to negatively affect the feasibility of the study.

The treatment consisted of the following four phases: (1) induction with 3–5 cycles of VAD (vincristine 0.4 mg IV, doxorubicin 9 mg/m^2 IV, and oral dexamethasone 40 mg daily for 4 days) every 21–28 days; (2) cyclophosphamide (4 g/m^2 IV) plus G-CSF (5 μg/kg twice a day) for stem cell mobilization; (3) melphalan (200 mg/m^2 IV) and ASCT; and (4) Randomization: maintenance therapy with arm A receiving dexamethasone alone (40 mg/d PO for 4 days every 28 days) or arm B receiving dexamethasone (same dose) plus thalidomide (200 mg PO daily) for 12 months or until disease progression.

Prophylaxis for deep venous thrombosis (DVT) was prescribed at the discretion of each investigator. The dose of thalidomide could be reduced if the patient experienced grade 2 or higher adverse events. In this case, thalidomide was discontinued and was restarted at a lower dose after the resolution of the adverse event. A bisphosphonate (clodronate, pamidronate, or zoledronate, depending on the center)

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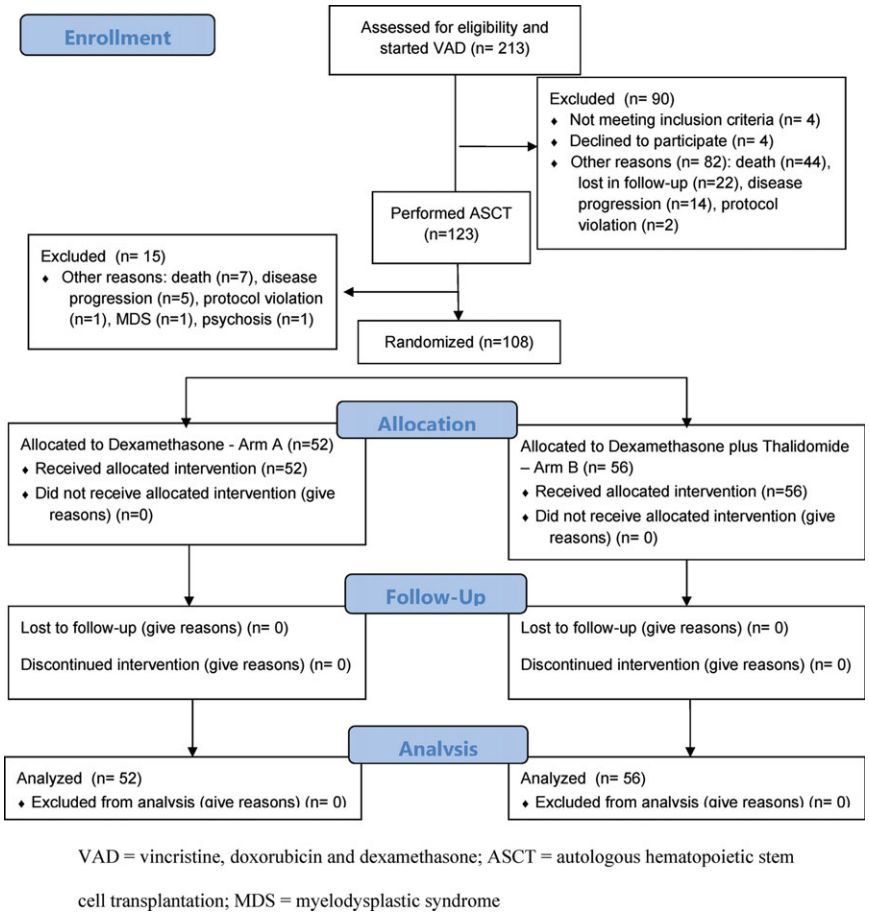

Figure 1. Consort chart of the trial based on the consolidated trial reporting standards. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

was given monthly for 24 months starting at the time of induction therapy.

The response to treatment was evaluated at the end of each phase of the protocol and every 3–4 months after randomization. The response was assessed using serum and urine M-protein levels as measured by electrophoresis and immunofixation. All of these parameters were assessed in a central laboratory. The criteria used to define response, relapse, and progression were taken from the European Group for Blood Marrow Transplantation, the International Bone Marrow Transplant Registry, and the Autologous Blood and Marrow Transplant Registry [7], with a very good partial response (VGPR) defined as a greater than 90% reduction in paraprotein levels (Inter-Groupe Francophone du Myélome, IFM) [8].

The objective of this study was to evaluate the efficacy of thalidomide plus dexamethasone as a maintenance therapy after ASCT. The primary endpoint was PFS, defined as the time from randomization until any documentation of relapse, progression, or death by any cause. The secondary endpoints were OS (defined as the interval from randomization to the last follow-up or death), and the tolerability and safety of thalidomide.

Response was assessed by the investigator and was centrally reviewed by an independent committee that was blinded to the study arm. In cases where there was a discrepancy between the investigator and the blinded committee, the committee's judgment prevailed.

Adverse events were classified according to the National Cancer Institute Common Toxicity Criteria, version 2. Safety evaluations were based on clinical features (medical history and physical examination) and focused especially on neurological symptoms and the development of DVT. Adverse event evaluations were performed at the time of response assessment and whenever a new clinical manifestation suggestive of toxicity appeared. Laboratory safety monitoring consisted of biochemical, hematological, and urine tests.

For sample size calculations, we considered a PFS of 40% in the dexamethasone arm [9] and 60% in the dexamethasone + thalidomide arm. Considering the values of $\alpha = 0.05$ and $\beta = 0.20$ and an expected loss of 15% from enrollment to randomization, 228 patients would be needed (114 patients per arm). Actuarial curves of OS and PFS were analyzed using the Kaplan-Meier method and were compared by the log-rank test. Categorical data were analyzed using the Chi-square or Fisher's exact tests as appropriate and continuous variables were compared using the Wilcoxon test. We looked at predictors of outcome (OS and PFS) by performing univariate Cox regression analysis and selected variables with P values <0.1 to enter into a multivariate Cox regression analysis. The following variables were analyzed: gender, age, Durie-Salmon stage, ISS, baseline hemoglobin, platelet, and leukocyte count, corrected calcium, β-2 microglobulin, creatinine, bone marrow plasmacytosis, chromosome 13 deletion (by FISH), response after VAD, ASCT, and maintenance, and the maintenance therapeutic arm (dexamethasone or dexamethasone + thalidomide). Two-sided P values <0.05 were considered statistically significant. Statistical analysis was performed using SPSS 15.0 software (SPSS).

Results

Two hundred and thirteen patients were enrolled and started the first phase of the protocol (VAD). The median age of the 213 patients was 55 years (range 27–71), and there were 110 males. Most patients had advanced disease at diagnosis (77% Durie-Salmon stage III, 71% ISS in stages II/III). Chromosome 13 deletion was present in 34% of the 150 patients tested.

Among the 213 patients, 123 (58%) underwent the scheduled ASCT, and 108 (51% of the enrolled patients and 88% of the patients who underwent ASCT) were randomly assigned to maintenance therapy: 52 in arm A and 56 in arm B (Fig. 1). Ninety patients did not undergo ASCT for the following reasons: early death ($n = 44$, including 36 deaths during VAD treatment phase and 8 during stem cell mobilization phase), lost in follow-up ($n = 22$), progression after VAD ($n = 14$), refusal ($n = 4$), not eligible for ASCT due to poor lung or cardiac function ($n = 4$), and

TABLE I. Baseline Characteristics of the 108 Patients Randomized to Receive Dexamethasone (Arm A; *n* = 52) or Dexamethasone + Thalidomide (Arm B; *n* = 56)

Variable	Arm A; *n* = 52	Arm B; *n* = 56	*P* value
Age (years); median (range)	55 (27–68)	52 (37–63)	0.052
Gender, male:female	29:23	30:26	0.82
Type of myeloma, *n* (%)			0.39
IgG	29 (56)	28 (50)	
IgA	13 (25)	15 (27)	
Light chain	10 (19)	10 (18)	
Nonsecretory	0	3 (5)	
Serum hemoglobin (g/dL), median (range)	10.4 (4.0–15.0)	9.9 (4.7–15.2)	0.67
Serum calcium (mg/dL), median (range)	9.3 (8.2–13.2)	9.4 (5.1–18.1)	0.56
Serum β-2-microglobulin (mg/dL), median (range)	2.72 (0.20–22.50)	2.86 (0.34–23.80)	0.80
Serum creatinine (mg/dL), median (range)	1.0 (0.5–8.0)	1.1 (0.6–5.7)	0.70
% Plasma cells in the bone marrow aspirate, median (range)	20 (13–100)	35 (13–95)	0.27
Chromosome 13 deletion, *n* (%)	9 (17)	13 (23)	0.45
Stage (Durie-Salmon), *n* (%)			0.86
IIA	10 (19)	12 (1)	
IIB	2 (4)	1 (2)	
IIIA	28 (54)	32 (58)	
IIIB	12 (23)	11 (19)	
International staging system, *n* (%)[a]			0.04
I	19/50 (38)	18/54 (33)	
II	16/50 (32)	29/54 (54)	
III	15/50 (30)	7/54 (13)	
Disease status after VAD regimen, *n* (%)			0.30
Complete or very good partial response	8 (15)	5 (9)	
Other[b]	44 (85)	51 (91)	
Disease status at randomization, *n* (%)			0.49
Complete or very good partial response	18 (35)	23 (40)	
Other[b]	34 (65)	33 (60)	
Time (days) from ASCT to randomization, median (range)	116.5 (52–162)	124.5 (30–181)	0.28

[a] Data available in 50 patients in arm A and 55 in arm B; VAD = vincristine, doxorubicin, and dexamethasone.

[b] Other includes partial remission, minimal response, and disease progression

TABLE II. Response Rate in Patients Receiving Dexamethasone (Arm A; *n* = 52) or Dexamethasone + Thalidomide (Arm B; *n* = 56)

Response	Arm A; *n* = 52	Arm B; *n* = 56	*P* value
After 12 months of maintenance			0.84
Complete or very good partial response	25 (48)	28 (50)	
Other[a]	27 (52)	28 (50)	
At last follow up			0.90
Complete or very good partial response	20 (38)	23 (40)	
Partial response/stable disease	3 (6)	4 (7)	
Progressive disease	29 (56)	29 (52)	

[a] Other includes partial remission, minimal response, and disease progression.

protocol violation (*n* = 2). Among the 123 ASCT recipients, 14 were not randomized for the following reasons: death (*n* = 7), disease progression (*n* = 5), concomitant myelodysplasia (*n* = 1), psychosis (*n* = 1), and protocol violation (*n* = 1).

Table I shows a comparison of the baseline characteristics of the 108 randomized patients. The two groups were comparable except for a higher median age in arm A (55 vs. 52 years; $P = 0.052$) and for a higher proportion of ISS stage III in arm A (30 vs. 13%; $P = 0.04$).

There were no differences in response rates (CR and VGPR) between the groups 12 months after the initiation maintenance therapy and at the last follow-up (Table II) in intention to treat analysis. After a median follow-up of 27 months, the estimated OS at 2 years was 70% in arm A (95% confidence interval [CI] 60–80) and 85% in arm B (95% CI 80–90; $P = 0.27$; Fig. 2A). The 2-year PFS was 30% in arm A (95% CI 22–38) and 64% in arm B (95% CI 57–71; $P = 0.002$; Fig. 2B), with median PFS of 19 months (range 15–22) and 36 months (range 22–49), respectively.

We looked at OS and PFS in good (CR and VGPR) and poor (below VGPR) responders after ASCT. The estimated OS at 2 years did not differ among good and poor responders (83% in arm A and 89% in arm B, $P = 0.41$, for good responders; 66% in arm A and 82% in arm B, $P = 0.29$, for poor responders). In contrast, patients who did not achieve a CR or VGPR, the estimated PFS at 2 years was significantly different between the two treatment groups (19% in arm A and 59% in arm B; $P = 0.002$; Fig. 3B). This difference was not observed in patients with CR or VGPR (Fig. 3A).

Multivariate predictors of PFS included the response after maintenance (hazard ratio [HR] 3.12, 95% CI 1.82–5.35; $P < 0.001$) and arm B (HR 2.43, 95% CI 1.43–4.13; $P = 0.001$). For OS, the only significant variable was baseline hemoglobin (HR 1.26, 95% CI 1.04–1.54).

Since there was an imbalance in the two arms regarding age and ISS stage, and considering that these variables may affect the primary endpoint, a Cox regression analysis was undertaken, including these two variables and the therapeutic arm only. In this model, the only significant variable was therapeutic arm B (HR 2.43, 95% CI 1.43–4.10, and $P = 0.001$).

Thalidomide was given to 49 of the 56 patients in arm B (87%) during the 12-month period. Forty-six patients (82%) received 200 mg during the study period. The median duration of thalidomide treatment in Arm B was 16 months (ranging from <1 to 51 months). Thalidomide was discontinued in 13 patients: three due to adverse events (neuropathy, DVT, and skin rash). Grade 3 or 4 adverse events occurred in four patients in arm A (8%) and in 19 in arm B (33%; $P = 0.001$). One patient from arm B experienced two adverse events. Peripheral neuropathy was observed in 12 patients receiving thalidomide (21%). Grade 3 or 4 DVT was reported in only one patient in arm B (Table III).

Discussion

In this study, even with fewer number of patients randomized than was target, we confirmed that the use of thalidomide in conjunction with corticosteroids following a single ASCT improves the PFS in patients with MM. The magnitude of this effect was greatest among patients who exhibited a poor response after ASCT.

Our PFS findings are similar to those found in previously published data evaluating the efficacy of a thalidomide-based regimen after ASCT [3,10–13]. Thalidomide has been used in MM patients since Barlogie et al. [5] and Singhal et al. [14] first demonstrated the beneficial activity of this drug in advanced and refractory disease. In addition, a powerful synergism between thalidomide and corticosteroids has been reported [15]. Maintenance treatment with thalidomide after ASCT was evaluated in a randomized trial by the IFM group [3]. The IFM 99-02 trial compared patients who did not receive maintenance therapy with those who received thalidomide plus pamidronate therapy after tandem ASCT and showed that the addition of thalidomide improved response rates as well as EFS and OS. Similar to this study, a greater benefit was observed in patients who had experienced a response less than VGPR at the time of randomization, suggesting that the benefit of thalidomide is to reduce the tumor mass rather than to maintain a response already obtained with prior therapy. Some differences in the two studies are worth mentioning. First, in the IFM trial, maintenance therapy was initiated after a tandem ASCT, whereas in this study, only one ASCT

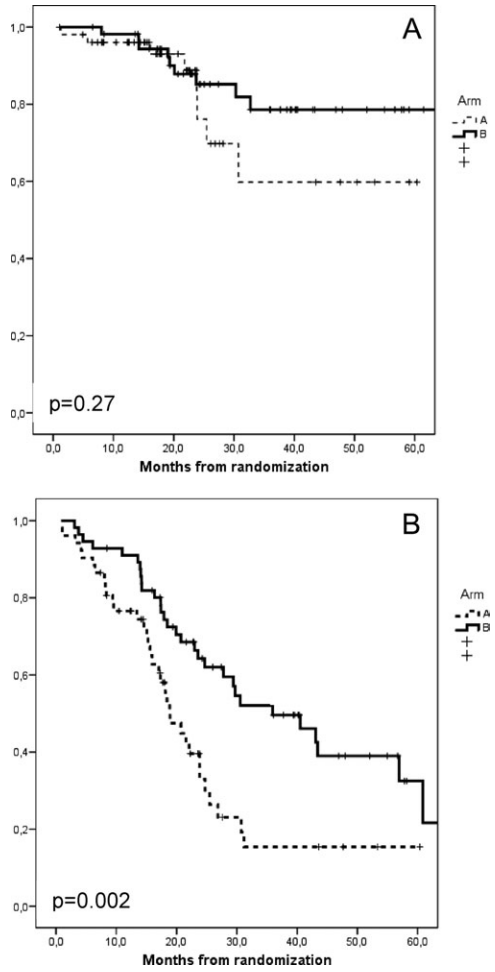

Figure 2. Overall survival (A) and PFS (B) for each treatment arm: Arm A: dexamethasone (n = 52) and Arm B: dexamethasone + thalidomide (n = 56). Kaplan-Meier survival curve with curve comparison using the log rank test.

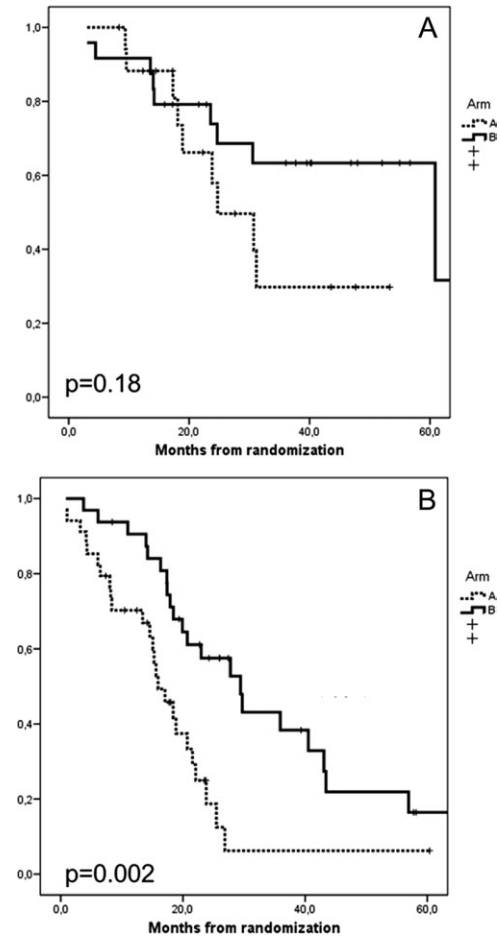

Figure 3. PFS according to the treatment arm and the disease status at randomization: (A) Complete response (CR) or very good partial response (VGPR) and (B) No CR or VGPR. Kaplan-Meier survival curve with curve comparison using the log rank test.

was performed. In addition, the IMF trial did not use dexamethasone. Finally, our study included all patients who met the inclusion criteria regardless of their prognostic risk (assessed by β-2 microglobulin serum level and the presence of chromosome 13 deletion), whereas the IFM trial included only low-risk patients [3].

A similar strategy using maintenance therapy with thalidomide after a single ASCT was reported by Spencer et al. In that trial, thalidomide was also combined with corticosteroids (in this case prednisolone), and this treatment resulted in prolonged PFS and OS. The benefit was observed in all patients independent of the response before randomization. Interestingly, the patients who did not achieve a response of CR or VGPR had longer PFS when thalidomide was added [4].

Two other randomized studies analyzed the impact of ASCT in conjunction with thalidomide in newly diagnosed MM patients, but these studies used different strategies [10,11]. In these trials, thalidomide was given before and after ASCT. Thalidomide improved response rates and prolonged EFS and PFS, but there was no benefit in terms of OS. The absence of an effect on OS was attributed to the fact that relapsed patients in the treatment arms without thalidomide received salvage therapy with this drug [10,11]. This is also the best explanation for the lack of an improvement in OS observed in our study.

Prolonged EFS or PFS may result in a benefit in OS as observed in a recent report of the long-term follow-up of two large clinical trials. In one trial (IFM 99-02), the survival benefit of thalidomide maintenance therapy that was reported in the original publication was no longer significant after 5.7 years of follow-up, but in the other trial (TT2), a significant benefit was observed after a median of 7.2 years of follow-up [16].

The impact of thalidomide maintenance therapy on the OS is definitely controversial. Stewart et al. reported a trial comparing thalidomide and prednisone versus observation alone after ASCT. In contrast to the other studies, OS was a primary endpoint in this trial. After a median follow-up period of 4 years, thalidomide maintenance therapy yielded an advantage for PFS, but not OS [13]. In another randomized trial that included both patients treated with ASCT and those who were not, thalidomide maintenance therapy was compared with observation only. Again, an advantage was observed for PFS but not OS. Recently, another trial with a larger number of patients showed again no benefits in terms of OS, but an impact on PFS. Furthermore, for high-risk patients defined by FISH, thalidomide maintenance was deleterious and yielded no advantage in PFS and a negative effect in OS [12]. These authors also performed a meta-analysis including their results and results of overall survival rates from IFM-9902, Spencer et al, TT2, and Ludwig et al. [3–5,17]. In this analysis, thalidomide had a significant late benefit in terms of OS, but any conclusion

TABLE III. Adverse Events According to Treatment Arm

	Adverse events grade 3 or 4	
	Dexa; *N* = 52 (%)	Dexa + Thal; *N* = 56 (%)
Peripheral neuropathy[a]	2 (4)	12 (21)
Fatigue	1 (2)	0
Constipation	0	4 (7)
Venous thrombosis	0	1 (2)
Rash/skin	1 (2)	1 (2)
Insomnia	0	1 (2)
Stroke	0	1 (2)

Dexa, dexamethasone; Thal, thalidomide; *P* value = 0.009.

must take account that these trials have important differences regarding ASCT and thalidomide strategy.

The rate of Grade III and IV adverse events in our trial was higher in the thalidomide arm, similar to other studies [3,4]. However, we observed a lower rate of thalidomide discontinuation due to adverse events as compared with these studies. While the reasons for these differences are not known, a possible explanation may be the fact that we strongly encouraged the investigators to reintroduce thalidomide at a lower dose as soon as symptoms improved.

Peripheral neuropathy is a major adverse event that limits prolonged maintenance with thalidomide. The introduction of lenalidomide has opened a new perspective because it has more potent immunomodulatory effects, and its use is not associated with peripheral neuropathy [18]. Indeed, lenalidomide maintenance after ASCT was explored in two large phase 3 trials. Both trials showed a clear benefit for lenalidomide versus placebo for PFS, with a very low incidence of peripheral neuropathy [19,20]. In one of these trials, there was a benefit for overall survival in the lenalidomide treatment arm [20]. An increased rate of second primary cancers was observed in the lenalidomide group in both studies.

A major limitation of our study is that almost half of the patients initially included in the study did not receive the scheduled ASCT and therefore were not randomized. The main cause of this loss was early death, related to infection in 60% of cases, and progression of myeloma in 32%. This is likely a reflection of the high proportion of patients in Brazilian hospitals with advanced disease at the time of diagnosis, as reported by Hungria et al. in a large retrospective epidemiologic study of MM [21]. In conclusion, a maintenance strategy using thalidomide and dexamethasone after a single ASCT significantly improves PFS in patients with MM. Additional studies are needed to assess whether this benefit is maintained with the incorporation of novel therapies.

Author Contributions

AM was the principal investigator and takes primary responsibility for the paper. VTMH, GOD, LCO, DRM, AAQ, ALMP, JCB, PT, RPM, EMR, ILM, and CC recruited the patients. CSPL, IZR, and EB performed the laboratory work. ECM, MG, and MN participated in the statistical analysis. ECM coordinated the research. AM, VTMH, MN, CAS, EMR, and MG drafted the manuscript. The authors report no conflicts of interest.

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