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ORIGINAL ARTICLE

Phase 3 trial of three thalidomide-containing regimens in patients with newly diagnosed multiple myeloma not transplant-eligible

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Abstract The introduction of agents such as thalidomide, lenalidomide, and bortezomib has changed the management of patients with multiple myeloma who are not eligible for autologous transplantation, many of whom are elderly. We sought to compare three thalidomide-based oral regimens among such patients in Latin America. We randomized patients with newly diagnosed multiple myeloma with measurable disease to one of the following regimens: melphalan, prednisone, and thalidomide (MPT); cyclophosphamide, thalidomide, and dexamethasone (CTD); and thalidomide and dexamethasone (TD). The TD arm was closed prematurely and was analyzed only descriptively. The primary endpoint was the overall response rate (ORR), whereas progression-free survival (PFS) and overall survival (OS) were secondary endpoints. The accrual rate was slower than expected, and the study was terminated after 82 patients had been randomized. The ORRs were 67.9 % with MPT, 89.7 % with CTD, and 68.7 % with TD (p=0.056 for the comparison between MPT and CTD). The median PFS was 24.1 months for MPT, 25.9 months for CTD, and 21.5 months for TD. There were no statistically significant differences in PFS or OS between MPT and CTD. In an unplanned logistic regression analysis, ORR was significantly associated with treatment with CTD (p=0.046) and with performance status of 0 or 1 (p=0.035). Based on the current results, no definitive recommendations can be made regarding the comparative merit of the regimens tested. Nevertheless and until the results of further studies become available, we recommend either CTD or MPT as suitable frontline regimens for patients with multiple myeloma who are not candidates to transplantation in settings where lenalidomide and bortezomib are not available.

Keywords Cyclophosphamide · Dexamethasone · Induction chemotherapy · Melphalan · Multiple myeloma · Thalidomide · Transplantation · Autologous · Survival analysis

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Introduction

In the USA, the median age at diagnosis among patients with multiple myeloma ranges between 65 and 71 years according to ethnic group [1]. For several years, the combination of melphalan and prednisone (MP) has remained a standard therapy for newly diagnosed, elderly patients with multiple myeloma [2], who are typically not eligible for high-dose chemotherapy and autologous transplantation [3]. More recently, the introduction of novel agents, such as thalidomide, lenalidomide, and bortezomib, has changed the management of this disease and challenged the role of MP alone. The combination of melphalan, thalidomide, and prednisone (MPT) has been shown to be superior to the standard MP in terms of the progression-free survival (PFS), in five out of six randomized trials, and overall survival (OS), in three out of six studies in newly diagnosed elderly patients with multiple myeloma [4–9]. These findings have been confirmed by a meta-analysis [10], and improved results in comparison with MP

alone have also been seen for the combinations of MP with both bortezomib [11] and lenalidomide [12]. Unfortunately, access to novel agents is limited under the current Brazilian public health system, despite its attempt to provide full and comprehensive care to citizens [13]. A similar situation in found other Latin American countries. On the other hand, thalidomide has been available at low costs in Brazil, Argentina, and several other Latin American countries for patients with multiple myeloma for several years. Moreover, the oral combination of cyclophosphamide, thalidomide, and dexamethasone (CTD) is active and safe in patients with relapsed [14] or newly diagnosed, transplant-ineligible [15] patients with multiple myeloma. Finally, thalidomide may be safely combined with dexamethasone (TD) [16], and this combination has led to improved response rates in comparison with melphalan/prednisolone among newly diagnosed elderly patients [17]. Thus, the objective of the present trial was to compare three thalidomide-based oral regimens (MPT, CTD, and TD) as frontline therapy for newly diagnosed patients with multiple myeloma who were not eligible for high-dose chemotherapy and autologous transplantation.

Methods

Study design and eligibility criteria

The current study (NCT01532856) was conducted in four centers in Brazil and one in Argentina. The study protocol was approved by the institutional review boards of all participating institutions, and written informed consent was obtained from all patients. This open-label, randomized trial with stratification by center started with three arms and a 1:1:1 randomization ratio; after 60 patients had been randomized, an unplanned interim analysis was conducted and suggested that the TD arm displayed inferior efficacy in terms of PFS, when compared with MPT and CTD. This same unplanned analysis suggested no differences between MPT and CTD with regard to efficacy endpoints. Despite the fact that no formal statistical rules were applied for such interim analysis, a decision was made to discontinue the TD arm, and randomization between MPT and CTD continued in a 1:1 ratio. Therefore, only descriptive results for the TD arm will be presented, whereas comparative results will be presented for the comparison between the MPT and CTD arms. After the induction treatment described herein, patients without disease progression and unacceptable toxicity were randomized to maintenance therapy with thalidomide alone or combined with prednisone, but the results pertaining to the maintenance phase will be the subject of a separate report.

For inclusion in the study, patients needed to have newly diagnosed, untreated multiple myeloma in stages II or III of the Durie-Salmon System (DSS), measurable disease confirmed by the presence of monoclonal protein in blood or Bence-Jones proteinuria, adequate hematological (absolute neutrophil count $\geq 1000/mm^3$, hemoglobin ≥ 8 g/dL, and platelet count $\geq 50{,}000/mm^3$, with lower values permitted if due to bone marrow infiltration) and biochemical parameters (serum creatinine ≤ 2 mg/dL, corrected serum calcium ≤ 14 mg/dL, aspartate and alanine transaminases ≤ 2.5 times the upper normal limit, and total bilirubin ≤ 1.5 times the upper normal limit), and ineligibility to undergo high-dose chemotherapy and autologous transplantation. Prior steroid pulses for treatment of myeloma-related emergencies, as well as bisphosphonates or radiation therapy, were permitted. The exclusion criteria were non-secretory multiple myeloma, positivity for HIV infection or hepatitis B virus, active hepatitis C virus infection, peripheral neuropathy higher than grade 2, life expectancy ≤ 12 weeks, history of other neoplasm other than non-melanoma skin cancer, myocardial infarction within 6 months prior to inclusion, any active cardiac disorder, or the presence of any condition that, in the opinion of the investigators, could pose undue risk to or compromise the ability to assess treatment results.

Treatment regimens

The composition of the three regimens were as follows: MPT, oral melphalan, 4 mg/m^2/day for seven consecutive days every 4 weeks, prednisone, 40 mg/m^2 for seven consecutive days every 4 weeks, and thalidomide, 200 mg/day continuously; CTD, oral cyclophosphamide, 50 mg/day continuously, thalidomide, 200 mg/day continuously, and dexamethasone, 40 mg/day on days 1 through 4 and 15 through 18 of the first two cycles, and for four consecutive days every 4 weeks thereafter; and TD, thalidomide, 200 mg/day continuously, and dexamethasone, 40 mg/day on days 1 through 4, 9 through 12, and 17 through 20 in odd-numbered cycles and on days 1 through 4 in even-numbered cycles. In all arms, cycles were repeated every 4 weeks for a maximum of nine cycles. In the three regimens, thalidomide was administered at the dose of 100 mg/day during the first 2 weeks to assess tolerance. Routine prophylactic measures were taken with regard to thrombosis and infections.

Assessment of endpoints

Response to treatment was assessed according to the International Myeloma Working Group criteria [18], with the best response for each patient categorized as complete response (CR), very good partial response (VGPR), partial response (PR), stable disease (SD), or disease progression (PD). The primary endpoint was the overall response rate (ORR), defined as at least a PR, and patients were assessed on day 1 of each cycle of induction and at the end of nine cycles. The secondary efficacy endpoints were PFS, defined as the interval

between randomization and the occurrence of death from any cause or disease progression, and OS, defined as the interval between randomization and death from any cause. Moreover, the frequency and severity of toxicity was secondary endpoint.

Statistical analysis

The sample size for the study was estimated with the expectation of finding an increase in 15 percentage points in ORR between either MPT or CTD and the TD arm, the latter with an expected ORR of 60 % [16]. Considering a two-sided type I error rate of 5 %, power of 80 %, and a dropout rate of 10 %, 100 patients would be required per arm. Response rates and other categorical variables were compared between groups using Fisher's exact test. Time-to-event endpoints were estimated by the Kaplan-Meier method, and differences between groups were compared using the log-rank test, with censoring of patients who were free of the corresponding outcomes of interest at the last date of contact. Logistic regression was used to assess the independent impact of covariates on ORR. Two-sided p values <0.05 were considered statistically significant. Statistical analysis was performed using MedCalc®, version 11.0.0.0 (Mariakerke, Belgium).

Results

Patient characteristics

The accrual rate was substantially slower than expected, and the study was terminated after 82 eligible patients had been randomized between July 2006 and April 2013. Moreover, the total number of patients was reduced, when compared with the target accrual, due to closure of the TD arm. Table 1 presents the main demographic and clinical features of the patients, whereas Fig. 1 displays the numbers of patients randomized and analyzed for the efficacy endpoints. Overall, nearly 56.1 % of patients were female, and the mean age was 72.2 years. The Eastern Cooperative Oncology Group (ECOG) performance status was 0 or 1 in 50.7 % of patients, DSS stage III was present in 86.1 % of cases, and 40.5 % of individuals had an International Staging System (ISS) stage of 3.

Treatment efficacy

Response to treatment is displayed in Table 2 for the 73 patients that were analyzed for response. Three patients (two from the MPT arm and one from the TD arm) did not complete the first treatment cycle, and for six additional patients, response data were missing. The ORRs were 67.9 % with MPT, 89.7 % with CTD, and 68.7 % with TD. The comparison between MPT and CTD yielded a p value of 0.056. In an unplanned, exploratory analysis of independent predictors of ORR, performance status of 0 or 1 was found to be significantly associated with response among patients treated with MPT or CTD in univariate analysis (p=0.036). In a logistic regression model, the outcome ORR was significantly associated with CTD treatment (p=0.046) and with performance status of 0 or 1 (p=0.035).

Table 1 Baseline patient characteristics

Characteristic	MPT (N=32)	CTD (N=32)	TD (N=18)
Mean age (years)	72.2	70.0	71.6
Female gender, %	53.1	65.6	44.4
Performance status, N (%)			
0 or 1	14 (43.8)	15 (46.9)	10 (55.6)
2	11 (36.7)	11 (37.9)	4 (22.2)
3 or 4[a]	5 (16.7)	4 (12.5)	4 (22.2)
Durie-Salmon System stage, N (%)[b]			
II	4 (13.3)	3 (9.7)	4 (22.2)
III	26 (86.7)	28 (90.3)	14 (77.8)
International Staging System stage, N (%)[b]			
1	6 (20.0)	8 (25.8)	3 (16.7)
2	10 (33.3)	10 (32.3)	10 (55.6)
3	14 (46.7)	13 (41.9)	5 (27.8)
Immunoglobulin (Ig) type, N (%)[b]			
IgA	9 (29.0)	7 (24.1)	4 (22.2)
IgG	16 (51.7)	16 (55.2)	10 (55.6)
IgM	0	1 (3.4)	0
Light chain	6 (19.4)	5 (17.2)	4 (22.2)

CTD cyclophosphamide, thalidomide, and dexamethasone, *Ig* immunoglobulin, *MPT* melphalan, prednisone, and thalidomide, *TD* thalidomide and dexamethasone

[a] There was a single patient (in the CTD arm) with performance status of 4

[b] Data were missing for some patients, and percentages refer to patients with non-missing data

Figure 2 shows the Kaplan-Meier curves for time-to-event endpoints after a median follow-up of 37.5 months. The median PFS times were 24.1 months for MPT, 25.9 months for CTD, and 21.5 months for TD. The hazard ratio for the comparison between MPT and CTD was 0.89 (95 % CI, 0.48 to 1.64; p=0.698; Fig. 2a). The median OS times were 42 months for MPT, 32.4 months for CTD, and 54.6 months for TD. The hazard ratio for the comparison between MPT and CTD was 1.08 (95 % CI, 0.54 to 2.19; p=0.821; Fig. 2b). At the time of analysis, 40 patients had died (15 in the MPT arm, 16 in the CTD arm, and 9 in the TD arm). When causes of death were analyzed, no significant differences were noted among the three arms (data not shown).

Toxicity

The frequency of selected adverse events is shown in Table 3. Although no formal statistical comparisons were

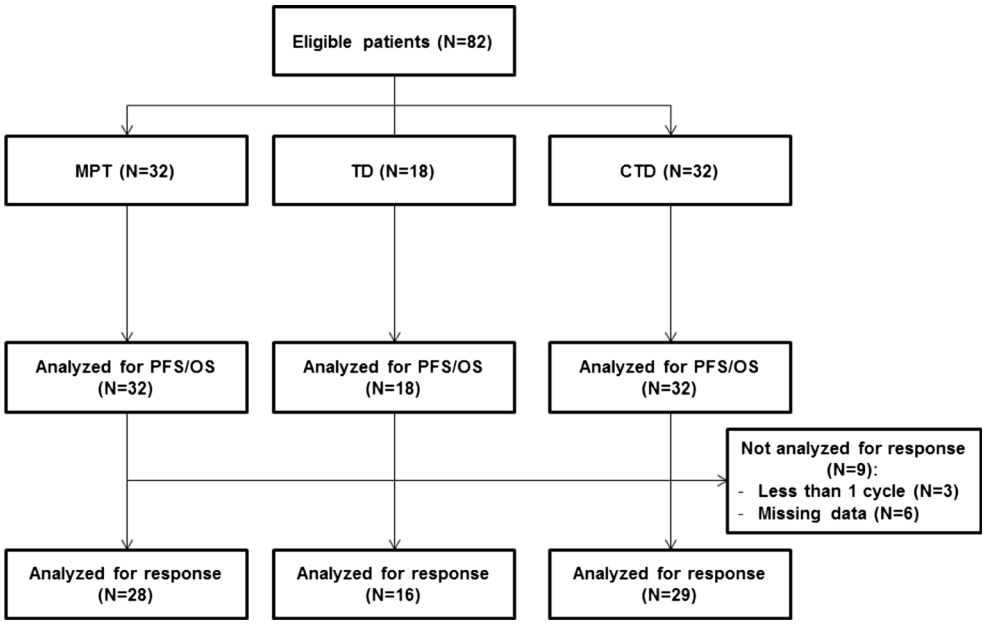

Fig. 1 Numbers of patients randomized and analyzed for the efficacy endpoints in each of the three study arms

undertaken, there were no differences in toxicity profile among the three arms. Treatment was discontinued due to an adverse event in a total of 18 patients (eight in the MPT arm, seven in the CTD arm, and three in the TD arm). There were two deaths on treatment: one due to liver toxicity after one cycle of CTD and one case of myocardial infarction during the seventh month of maintenance with thalidomide in a patient randomized to TD. Grading of adverse events was only available for anemia, neutropenia, thrombocytopenia, neuropathy or tremor, and constipation. As shown in Table 4, grade 3 or 4 neutropenia appeared more frequent with MPT and CTD than with TD, grade 3 or 4 neuropathy or tremor was more frequent with MPT than with the other two treatments, and the grade distribution of other adverse events was nearly similar across treatment arms. Dose modifications due to adverse events were relatively frequent along therapy. Depending on the cycle considered, dose modifications were required in 6 to 11 patients per cycle in the MPT arm, 7 to 11 patients per cycle in the CTD arm, and 1 to 5 patients per cycle among those treated with TD. Thalidomide dose reductions or complete discontinuation of the combination regimen were required in 20 patients in the MPT arm, 18 in the CTD arm, and 9 in the TD arm.

Table 2 Selected efficacy results

Efficacy endpoint	MPT	CTD	*p* Value (MPT vs CTD)	TD
Response to treatment, %				
Complete response	14.3	20.7		12.5
Very good partial response	25.0	34.5		18.7
Partial response	28.6	34.5		37.5
Stable disease/progressive disease	21.4/10.7	10.3/0		31.3/0
Overall response rate	67.9	89.7	0.056	68.7
Progression-free survival				
Median, months	24.1	25.9		21.5
Hazard ratio[a]	0.89		0.698	
Overall survival				
Median, months	42.0	32.4		54.6
Hazard ratio[a]	1.08		0.821	

CTD cyclophosphamide, thalidomide, and dexamethasone, *Ig* immunoglobulin, *MPT* melphalan, prednisone, and thalidomide, *TD* thalidomide and dexamethasone

[a] Hazard ratios are for comparisons between MPT and CTD

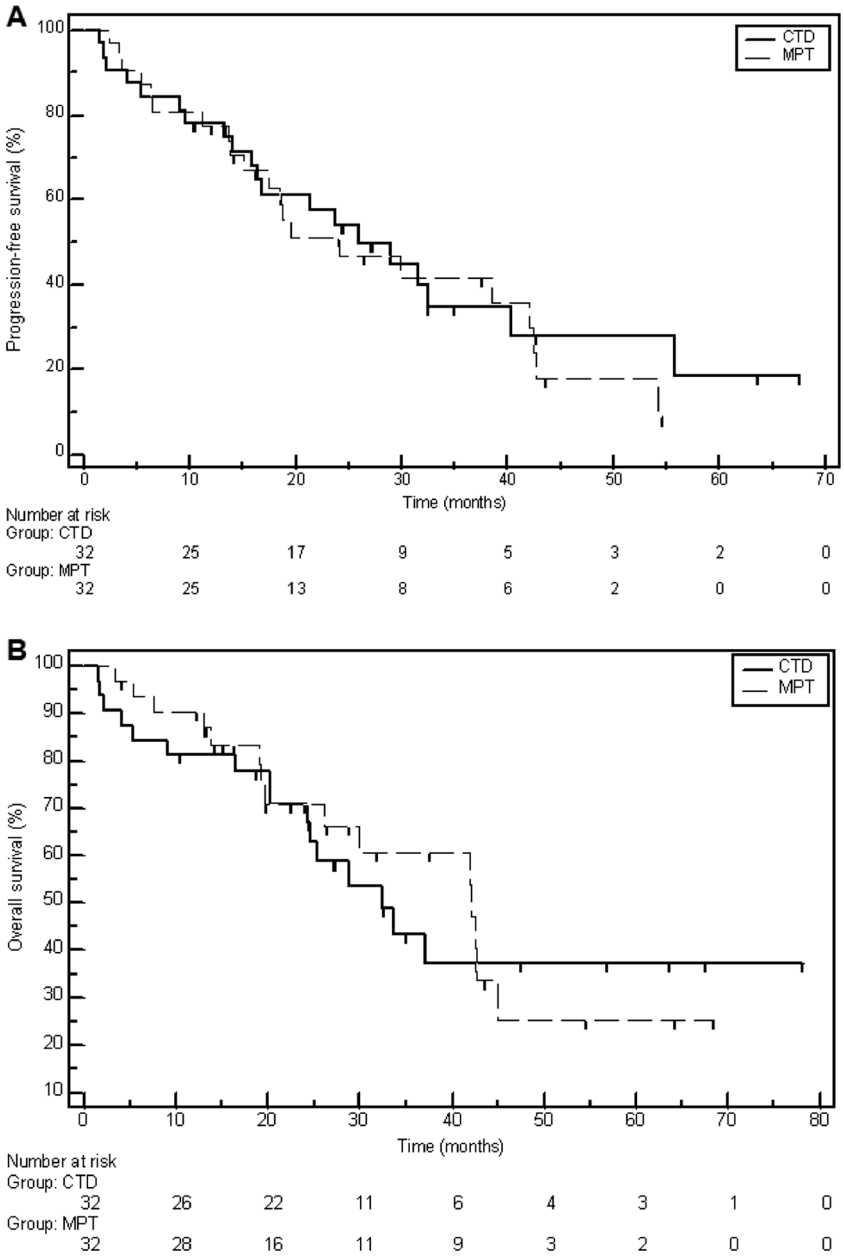

Fig. 2 Progression-free survival (**a**) and overall survival (**b**) among patients treated with melphalan, thalidomide, and prednisone (MPT) or cyclophosphamide, thalidomide, and dexamethasone (CTD). *Tick marks* represent censoring

Table 3 Profile of adverse events

Adverse event, *N* (%)	MPT *N*=32	CTD *N*=32	TD *N*=18
Anemia	7 (21.9)	8 (25.0)	6 (33.3)
Febrile neutropenia	0	2 (6.2)	0
Neutropenia	12 (37.5)	10 (31.2)	4 (22.2)
Thrombocytopenia	1 (3.1)	0	2 (11.1)
Neuropathy or tremor	14 (43.7)	14 (43.7)	7 (38.9)
Constipation	7 (21.9)	12 (37.5)	6 (33.3)
Thrombosis	2 (6.2)	3 (9.4)	2 (11.1)
Pneumonia	4 (12.5)	5 (15.6)	4 (22.2)

CTD cyclophosphamide, thalidomide, and dexamethasone, *MPT* melphalan, prednisone, and thalidomide, *TD* thalidomide and dexamethasone

Discussion

The current multicenter trial conducted in Brazil and Argentina did not meet its accrual goal; not only was accrual slower than expected, but closure of the TD arm further compromised the final number of patients. As a result, the trial is underpowered to detect meaningful differences in ORR among the three arms. Moreover, the trial is severely underpowered to detect plausible differences in PFS or OS, secondary endpoints in the study which typically require a larger number of patients and longer follow-up. Nevertheless, a borderline difference in ORR of slightly over 20 percentage points was found between CTD and MPT, the two trial arms onto which accrual continued after an unplanned interim analysis that led to closure of

Table 4 Grading of selected adverse events

Adverse event, *N*		MPT (*N*=32)		CTD (*N*=32)		TD (*N*=18)	
	Grade[a]	1/2	3/4	1/2	3/4	1/2	3/4
Anemia		4 (13.3)	1 (3.3)	4 (12.9)	3 (9.7)	2 (12.5)	2 (12.5)
Neutropenia		1 (3.1)	11 (34.4)	4 (12.5)	6 (18.8)	3 (16.7)	1 (5.6)
Thrombocytopenia		1 (3.1)	0	0	0	2 (11.1)	0
Neuropathy or tremor		8 (25.0)	6 (18.8)	13 (40.6)	1 (3.1)	4 (22.2)	3 (16.7)
Constipation		5 (15.6)	2 (6.3)	9 (28.1)	2 (6.3)	5 (29.4)	0

CTD cyclophosphamide, thalidomide, and dexamethasone, *MPT* melphalan, prednisone, and thalidomide, *TD* thalidomide and dexamethasone

[a] Grading was not available for five patients in the case of anemia and for one patient in the case of constipation; for this reason, percentages in the table consider only patients with available data in the denominator

the TD arm. However, such nominally improved response rates did not translate into improved long-term outcomes, as shown by the PFS and OS analyses (Table 2). Indeed, OS results were nominally inferior with CTD than with MPT, with nearly a 10-month difference in medians favoring MPT. This difference may well represent the play of chance, as the hazard ratio for this OS comparison was close to 1.00. However, the extent to which OS may have influenced by salvage therapies remains undetermined.

The efficacy results of the current trial may be compared with those from similar studies reported in the past. The ORRs found in this study are in the range of response rates reported in phase II and III trials among elderly patients treated with combinations containing thalidomide, lenalidomide, and bortezomib [4, 11, 12, 15, 17, 19]. Likewise, the results for median PFS and OS observed in the current trial are similar to those from previously reported results with MPT and CTD [10, 15, 20]. Of note, our median PFS with MPT (24.1 months) compares favorably with the median PFS times reported for the FIRST trial. The median PFS times found in our study for MPT and CTD are also similar to the median time to progression reported for the combination of bortezomib plus MP in the VISTA study [11]. For TD, our median PFS results are in line with the median time to progression reported by Rajkumar et al. for this same regimen (22.6 months) [19]. On the other hand, the median OS found in the current trial for the TD arm (54.6 months) is higher than in many previous trials among this patient population; the extent to which this finding is confounded by other factors remains uncertain. Given the track record of both MPT and CTD in the literature, and the nominally inferior results for PFS found for TD in the current trial, we do not recommend TD as a standard frontline regimen.

This investigator-initiated study clearly exemplifies the challenge of conducting clinical trials in Latin America and probably other world regions where resources are scarce and where most of the investment is made toward industry-sponsored trials. The lower-than-expected accrual rate compromised our ability to reach definitive conclusions about the comparative merit of three regimens commonly used in Latin America. Despite these limitations, to our knowledge, this is the first published randomized trial comparing MPT and CTD, two potentially useful combinations for use in patients with newly diagnosed multiple myeloma. Both of these combinations are feasible in countries with scarce health care resources, like Brazil and other Latin American countries where thalidomide has been available at low cost for more than a decade. Such feasibility was demonstrated in previous studies [5, 10, 14, 15] and was confirmed by the present results. Moreover, these are oral therapies and as such may be attractive to both patients and health services.

The main value of our study lies in the assessment of three different thalidomide-containing arms among transplantation-ineligible patients who would not otherwise receive other agents, such as bortezomib, lenalidomide, or even more novel representatives of these drug classes. Such agents remain unavailable to patients treated under the public health system in Brazil, where arguably nearly two thirds of Brazilian patients with multiple myeloma are treated, and similar situations are found in other Latin American countries. Particularly in elderly patients with multiple myeloma, the outlook is improving with novel therapies, but efficacy must be balanced with the risk of toxicity and quality-of-life issues [21].

Unfortunately, no definitive conclusions can be drawn regarding the comparative merit of the three regimens.

Considering the overall efficacy results from the present study, it seems that both CTD and MPT are valid regimens for patients with a similar eligibility profile, whereas conclusions on the efficacy of TD cannot be drawn at the present time. With regard to safety results, none of the three regimens appears superior, although the severity of neutropenia appeared slightly higher with CTD and that of neuropathy with MPT. Until the evidence base for the treatment of this patient population is increased, we recommend either CTD or MPT as suitable frontline regimens for transplant-ineligible patients with multiple myeloma in settings where other novel agents are not available. However, with the recent trend for continued rather than fixed-duration therapy [20], there is a pressing

need to identify regimens with no cumulative toxicity and an improved efficacy profile.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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