

Dose-dependent Effect of Thalidomide on Overall Survival in Relapsed Multiple Myeloma

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ABSTRACT

Purpose: Although thalidomide (Thal) was introduced successfully in the treatment of multiple myeloma (MM), the optimal Thal dosage and schedule are still controversial. The aim of this study was to analyze whether the effect of Thal in MM is dose dependent and whether the outcome might be improved when the Thal dosage is adjusted to parameters reflecting body size.

Experimental Design: From December 1998 to March 2001, 83 patients with relapsed MM were enrolled in a clinical Phase II trial and treated with a maximum Thal dosage of 400 mg daily. We performed a retrospective analysis and studied the effect of the cumulative 3-month Thal dosage on progression-free survival and overall survival (OS) together with age and the pretreatment levels of β_2 -microglobulin, C-reactive protein, albumin, and hemoglobin in a Cox regression model.

Results: After a median follow-up time of 17 months (range, 1–30 months), the estimated 12-month progression-free survival and OS were 45% (SE = 6%) and 86% (SE = 4%) for the whole patient group. After backward selection, hemoglobin ($P = 0.002$) and the cumulative 3-month Thal dosage ($P = 0.002$) were the remaining factors for OS. The effect on OS could not be improved when the cumulative 3-month Thal dosage was adjusted to parameters reflecting body size such as height, weight, body surface area, or body mass index in comparison with Thal alone.

Conclusions: Our retrospective analysis demonstrates that the cumulative 3-month Thal dosage is one of the major prognostic factors for OS, supporting the hypothesis of a dose-dependent effect of Thal in relapsed MM.

INTRODUCTION

In recent years, Thal² has been introduced successfully in the treatment of MM. Singhal *et al.* (1) conducted the first clinical trial and used Thal as a single agent in refractory and relapsed MM, resulting in a response rate of 32% as evidenced by a reduction of monoclonal protein of at least 25%. The rationale for the use of Thal in MM was based on laboratory studies showing that Thal inhibits angiogenesis in a rabbit cornea micropocket assay (2). Recently, our group has reported that high pretreatment levels of the proangiogenic cytokine basic fibroblast growth factor were found to be associated with response to Thal therapy in progressive MM (3). However, decrease of bone marrow microvessel density and reduction of angiogenic cytokine levels were not consistently found in all Thal-responsive PTs (1, 4), indicating that Thal does not mediate its anti-MM activity through its antiangiogenic properties alone. Raje and Anderson (5) proposed that Thal might also act by a variety of additional mechanisms, direct effects on survival and growth of myeloma cells, modulation of the cytokine milieu in the BM, or alteration of the profile of adhesion molecules. Recently, Davies *et al.* (6) demonstrated that Thal acts as a costimulator to trigger proliferation of anti-CD3-stimulated T-cells from MM PTs. In these PTs, an increase in the percentage of natural killer cells was associated with response to Thal therapy (6).

Although Thal and its analogues act by a direct dose-dependent effect on MM cell lines and in PT MM cells that were resistant to melphalan, doxorubicin, and dexamethasone (7), the clinical use of high Thal dosages is limited by the toxicity of Thal. In the study of Barlogie *et al.* (8) including 169 MM PTs with refractory and relapsed disease, Thal was started at a dose of 200 mg daily, and the dose was increased by 200 mg every 2 weeks until a dose of 800 mg/day was reached. Only 56% of all PTs tolerated a Thal dose of 800 mg/day. Toxicity of >grade 2 was observed in 58% of all PTs, affecting the central nervous system in 25% of PTs, the gastrointestinal tract in 16% of PTs, and the peripheral nerves in 9% of PTs. These toxicities were related to the cumulative dose of Thal administered. Because initial response occurred early within 1 month after the start of Thal therapy, and dose escalation significantly increased toxicity during Thal treatment (1, 8), the efficacy of lower Thal dosages from 50–400 mg/daily has been studied recently by Durie and Stepan (9), resulting in a response rate of 44% in a group of 36 PTs. Of note, two PTs who are in remission over 30 months received the lowest Thal doses of 50 mg/day. However,

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² The abbreviations used are: Thal, thalidomide; MM, multiple myeloma; PFS, progression-free survival; OS, overall survival; HDT, high-dose chemotherapy; PBSCT, peripheral blood stem cell transplantation; PT, patient.

clinical Phase III studies of Thal in MM are still missing, and the optimal Thal dose and schedule are controversial.

To study whether Thal action in MM is dose dependent, we decided to perform a retrospective analysis in a group of 83 PTs with relapsed MM who were treated with a maximum Thal dosage of 400 mg daily. The effect of the Thal dose was compared to well-characterized predictors of response and survival in MM such as β 2-microglobulin (10), C-reactive protein (10), albumin (11), and hemoglobin (12). Because previous Thal treatment schedules did not consider parameters reflecting body size, we also examined whether an adjustment of the Thal dosage to parameters such as height, body weight, body mass index, and body surface area improves the outcome of Thal therapy.

PATIENTS AND METHODS

Treatment Design. From December 1998 to March 2001, 83 PTs with relapsed MM were enrolled in a clinical Phase II trial and treated with Thal. The study has been approved by the ethical guidelines of the Joint Committee of Clinical Investigation of the University of Heidelberg. All PTs had to sign an informed consent form indicating the potential benefit and toxicities associated with the treatment. Thal was supplied in 100-mg tablets by Gruenthal GmbH (Aachen, Germany). At the start of Thal treatment, the drug was administered at a dose of 100 mg daily, followed by a weekly dose increase of 100 mg daily for a final dose of 400 mg daily beginning at day 22.

Laboratory and Clinical Evaluation. The pretreatment and monthly follow-up evaluations included full blood counts; renal and liver function tests; serum levels of immunoglobulins, β 2-microglobulin, lactate dehydrogenase, and C-reactive protein; Bence Jones protein in urine; and serum and urine protein electrophoresis. Bone marrow aspirations were performed in the PTs before ($n = 65$) and 3 ($n = 51$) and 6 months ($n = 41$) after the start of Thal treatment to determine the percentage of plasma cells. X-rays of the skull, thorax, spine, pelvis, humera, and femora were obtained before treatment and every 6 months during treatment to assess the number and size of bone lesions. For the evaluation of adverse effects, the WHO system of classification was used. All PTs were evaluated for response monthly. If PTs had detectable levels of monoclonal protein in urine and serum, then response was evaluated on the component showing the smaller decline. New lytic lesions (but not compression fractures), hypercalcemia, an increase in monoclonal protein of more than 25% from nadir, or other new evidence of disease constituted progressive disease. Disease progression and death from any cause were the only events that accounted for PFS.

Statistical Analysis. Survival probabilities were estimated by the Kaplan-Meier method. Primary end points of the study were PFS and OS. The median follow-up duration was estimated according to the method of Korn (13). For multiple regression analysis, we concentrated on age, well-characterized predictors for response and survival in MM (β 2-microglobulin, hemoglobin, albumin, and C-reactive protein), and the cumulative Thal dosage within the first 3 months of treatment. To evaluate the effect of these six variables on PFS and OS, a

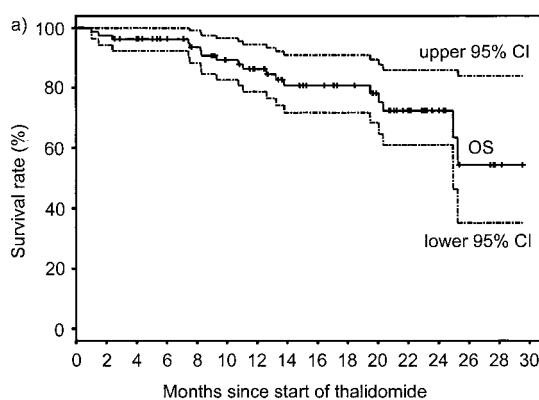
multivariate analysis (Cox proportional hazards regression) was performed. Body size parameters (body weight and height, body surface area, and body mass index) had been determined at the start of Thal therapy and were extracted from the hospital records. Body mass index was calculated by dividing body weight by the squared value of height (kg/m^2). To study the impact of parameters reflecting body size on the outcome of Thal therapy, each of these factors was added separately to the Cox proportional hazards regression analysis consisting of age, β 2-microglobulin, hemoglobin, albumin, and C-reactive protein. To analyze whether sex, age, and baseline levels of albumin, hemoglobin, β 2-microglobulin, and C-reactive protein are prognostic factors for achieving at least 3 months of Thal treatment, a logistic regression analysis was performed. An effect was considered as statistically significant if the P of its corresponding statistical test was $<5\%$. The statistical analyses were performed using the software packages StatXact (Cytel Software Corp., Cambridge, MA) and S-Plus (Insightful, Inc., Seattle, WA) together with the Design software library.

RESULTS

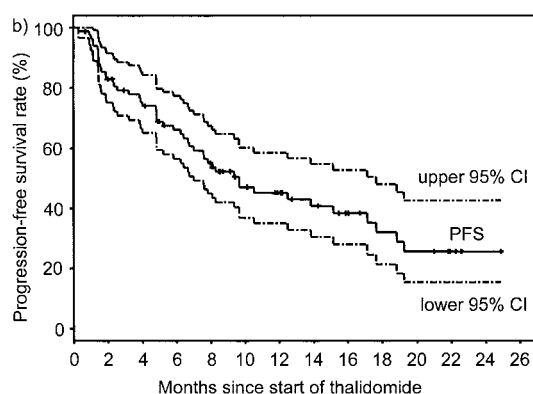
PT Characteristics. According to the classification system of Salmon and Durie, 6 PTs had stage II MM, and 77 PTs had stage III MM. There were 61 males and 22 females with a median age of 59 years (range, 34–86 years). The median time from diagnosis to entry into the study was 37 months (range, 12–191 months). All 83 PTs received chemotherapy before Thal, including a median number of 7 (range, 3–30 cycles) chemotherapy cycles and at least 1 cycle of HDT and PBSCT in 60 PTs. Before Thal, all PTs had progressive disease according to the European Bone Marrow Transplantation Group criteria (14). The median interval from the last chemotherapy to the start of Thal was 12 months (range, 3–65 months). In particular, the last treatment before Thal was as follows: 27 PTs were treated with conventional chemotherapy; 30 PTs received 1 cycle of HDT and PBSCT; 25 PTs received 2 cycles of HDT and PBSCT; and 1 PT received 3 cycles of HDT and PBSCT. The PT characteristics are summarized in Table 1.

Table 1 PT characteristics of 83 PTs with relapsed MM

A. Characteristic	No. of PTs
Male	61 (73%)
Stage III (Salmon and Durie classification)	77 (93%)
IgG monoclonal protein	43 (52%)
IgA monoclonal protein	25 (30%)
κ light chain	61 (73%)
Prior HDT	60 (72%)
No. of HDT cycles > 1	26 (31%)
B. Characteristic (normal range)	Median (range)
Age (yrs)	59 (34–86)
No. of pretreatment chemotherapy cycles	7 (3–30)
Hemoglobin (12–17 g/dl)	11.6 (7.3–15)
Platelets (150–450/nl)	200 (11–544)
Serum albumin (30–50 g/liter)	41 (26–59)
Serum calcium (2.1–2.65 mmol/liter)	2.39 (1.72–2.89)
Serum β 2-microglobulin (≤ 2.5 mg/liter)	3.2 (1.3–96.8)
Serum C-reactive protein (≤ 5 mg/liter)	3.8 (< 2 –128)



Number at risk: 83 81 78 72 67 59 52 41 37 32 27 19 11 5 2 0



Number at risk: 83 68 59 48 39 27 23 18 14 10 8 4 2 0

Fig. 1 OS (a) and PFS (b) for 83 PTs with relapsed MM after initiating treatment with Thal. In addition, the 95% confidence interval is shown. The estimated 12-month PFS and OS were 45% (SE = 6%) and 86% (SE = 4%) for the whole PT group.

Survival Analysis. The median follow-up time was 17 months (range, 1–30 months), the estimated 12-month PFS and OS were 45% (SE = 6%) and 86% (SE = 4%) for the whole PT group (Fig. 1). Thus far, 18 PTs have died, 7 were nonresponsive to Thal, and 11 died with progressive disease after initial response. According to the criteria of the European Bone Marrow Transplantation Group (14), 18 PTs achieved a minimal response, 16 PTs achieved a partial response, and 1 PT achieved a complete response, resulting in an overall response rate of 42%. The median time from start of Thal therapy to response was 3 months (range, 1–7 months), respectively.

Thal Dosage and Toxicity. Thal could be escalated to 200, 300, and 400 mg in 100%, 92%, and 82% of PTs, respectively (Fig. 2). In 70 of 83 PTs (84%), the daily Thal dosage had to be reduced. After 3 months of Thal treatment, 38 of 70 PTs (54%) received a daily Thal dosage of 400 mg, after 6 months of Thal treatment, 16 of 48 PTs (33%) received a daily Thal dosage of 400 mg, after 9 months of Thal treatment, 8 of 33 PTs (24%) received a daily Thal dosage of 400 mg, and after 12 months of Thal treatment, 4 of 23 PTs (17%) received a daily Thal dosage of 400 mg. Thal-associated WHO grade 1 and 2 adverse effects were in the same range as reported previously

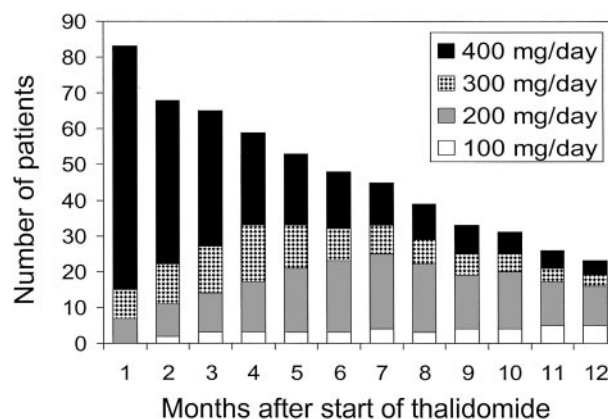


Fig. 2 Among all 83 PTs, the maximum dosage of Thal that was tolerated by each individual PT monthly is shown. Thal could be escalated to 200, 300, and 400 mg in 100%, 92%, and 82% of PTs, respectively. In 70 of 83 PTs (84%), the daily Thal dosage had to be reduced over time.

Table 2 Grade 3 and 4 toxicity according to the classification of the WHO among 83 Thal-treated PTs

Adverse effects	No. of PTs	
	Grade 3	Grade 4
Infection	5 (5%)	2 (2%)
Tingling or numbness	5 (6%)	
Deep venous thrombosis	3 (4%)	
Syncope	2 (2%)	
Cardiac function ^a	2 (2%)	1 (1%)
Hearing disturbance	1 (1%)	
Leukocytopenia	1 (2%)	

^a Preexisting congestive heart failure that worsened after initiation of Thal therapy ($n = 2$); myocardial infarction ($n = 1$).

(3), including somnolence (51%), constipation (48%), dryness of mouth (42%), tingling or numbness (36%), fatigue or weakness (36%), tremor (33%), infection (24%), dizziness (24%), rash (14%), and mood changes (12%). Grade 3 and 4 toxicities are summarized in Table 2 and were observed in 22 PTs (27%). The median time from the initiation of Thal therapy to the presence of WHO grade 3 and 4 toxicities was 3 months (range, 1–12 months). Adverse effects attributed to Thal resulted in a dose reduction in 72% of PTs and discontinuation of Thal in 14% of PTs. No treatment-related deaths were observed.

Early Treatment Failure Analysis. In 14 of 83 PTs, Thal therapy was discontinued within the first 3 months of treatment. The reasons were as follows: 6 PTs had progressive disease and continued treatment with a combination of Thal and conventional chemotherapy (15); 4 PTs could not tolerate Thal; and 4 PTs died with progressive disease without showing a response to Thal therapy. To analyze whether sex, age, and baseline levels of albumin, hemoglobin, β 2-microglobulin, or C-reactive protein are prognostic factors for achieving at least 3 months of Thal treatment, a logistic regression analysis was performed. In the final model, only age ($P = 0.005$) remained as a statistically significant factor. This group of 14 PTs had a

Table 3 Multivariate analysis of prognostic markers for PFS and OS (Cox proportional hazards regression)
The data set includes 69 PTs with relapsed MM who were treated with Thal for at least 3 months.

	Interval analyzed ^a	Estimated hazard ratio	95% Confidence interval	P
PFS				
β2-Microglobulin (mg/liter)	2.5–5.0	1.40	0.96–2.04	0.08
Albumin (g/liter)	35–45	0.82	0.33–1.99	0.66
Hemoglobin (g/dl)	9–12	0.89	0.40–1.99	0.78
C-reactive protein (mg/liter)	2–5	0.78	0.37–1.67	0.53
Age (yrs)	50–65	0.52	0.25–1.08	0.08
Thal	19.8–31.8	0.62	0.25–1.53	0.30
OS				
β2-Microglobulin (mg/liter)	2.5–5.0	1.41	0.73–2.72	0.30
Albumin (g/liter)	35–45	0.67	0.13–3.43	0.63
Hemoglobin (g/dl)	9–12	0.20	0.06–0.70	0.01
C-reactive protein (mg/liter)	2–5	0.37	0.09–1.60	0.19
Age (yrs)	50–65	0.87	0.26–2.97	0.83
Thal	19.8–31.8	0.07	0.01–0.37	0.001

^a In this statistical model, the effect on PFS and OS was analyzed for the indicated intervals of β2-microglobulin, albumin, hemoglobin, C-reactive protein, age, and the cumulative 3-month Thal dosage. These intervals are defined by the borderlines to the upper and lower quartiles. Additional parameters such as myeloma stage or type did not show a relevant effect in this statistical model.

median age of 68 years (range, 51–83 years), whereas the median age of all other PTs was 58 years (range, 34–86 years).

Cumulative 3-Month Thal Dosage and Outcome. The cumulative 3-month Thal dosage was calculated in 69 PTs who received Thal for at least 90 days. The effect of the cumulative 3-month Thal dosage on PFS and OS was studied in a multivariate analysis (Cox regression model) together with age and the pretreatment levels of β2-microglobulin, C-reactive protein, albumin, and hemoglobin. As shown in Table 3, the cumulative 3-month Thal dosage ($P = 0.001$) as well as the hemoglobin level ($P = 0.01$) had a statistically significant effect on OS. After backward selection, β2-microglobulin ($P = 0.02$) was the remaining factor for PFS, whereas both the cumulative 3-month Thal dosage ($P = 0.002$) and hemoglobin level ($P = 0.002$) remained in the final model for OS.

To illustrate the effect of the cumulative 3-month Thal dosage on survival after Thal therapy, predicted PFS and OS as derived from the multivariate analysis are shown in Fig. 3. After 18 months of treatment, the PT group tolerating the maximum Thal dose of 400 mg daily (cumulative 3-month Thal dose of 31.8 g) had a 15–20% higher predicted PFS and OS as compared with PTs with a dose reduction from 400 to 200 mg after the first month of Thal therapy (cumulative 3-month Thal dose of 19.8 g).

Body Size and Thal Dosage. To study whether the effect on PFS and OS could be improved when the cumulative 3-month Thal dosage was related to parameters reflecting body size, each of the following factors was added separately to the Cox regression model described in Table 3: Thal/height; Thal/body mass index; Thal/body surface area; and Thal/body weight. As shown in Table 4, an adjustment of the Thal dose to parameters reflecting body size could not improve the outcome after Thal therapy in comparison with Thal alone.

DISCUSSION

In our retrospective analysis of 83 PTs with relapsed MM, the cumulative 3-month Thal dosage is one of the major prognostic factors for OS, compared with well-characterized predic-

tors of response and survival in MM such as β2-microglobulin, C-reactive protein, albumin, and hemoglobin. This finding supports the hypothesis of a dose-dependent effect of Thal in MM. The effect on OS could not be improved when the cumulative 3-month Thal dosage was adjusted to parameters reflecting body size such as height, weight, body surface area, or body mass index in comparison with Thal alone, suggesting the use of previously introduced treatment schedules (1, 9, 16), independent of parameters reflecting body size.

Our study protocol is in line with Durie and Stepan (9), using a maximum Thal dosage of 400 mg daily, whereas a higher dosage of 800 mg is aimed at in the studies by Singhal *et al.* (1) and Rajkumar *et al.* (16). Independent of the maximum Thal dosage, all studies show comparable response rates, varying from 32% (1) to 44% (9). This is probably related to a different PT selection and response criteria used for evaluation. Of importance, the median interval between the start of treatment and a decrease in the monoclonal paraprotein level of at least 25% was 3 months in our study, whereas Singhal *et al.* had already achieved this result after 1 month (1), a difference that might be explained by the use of a more dose-intensive treatment schedule.

As shown in the present study, the PT group tolerating the maximum Thal dose of 400 mg daily (cumulative 3-month Thal dose of 31.8 g) had a 15–20% higher predicted PFS and OS after 18 months of treatment as compared with PTs with a dose reduction from 400 to 200 mg after the first month of Thal therapy (cumulative 3-month Thal dose of 19.8 g). Probably as a statistical effect of a longer follow-up time, we found a more profound dose-dependent Thal effect on OS than on PFS. Consistently, Barlogie *et al.* (8) performed a landmark analysis after 3 months, finding a superior 2-year survival of 63% versus 45% for PTs tolerating a cumulative 3-month dosage of >42 g. In this study, a better OS was also found in PTs with normal cytogenetics, plasma cell labeling index ≤ 0.5 , β2-microglobulin ≤ 3 mg/liter, and C-reactive protein ≤ 7 mg/liter. The clinical findings of a dose-dependent Thal effect in MM are in line with laboratory observations. Hideshima *et al.* (7) found

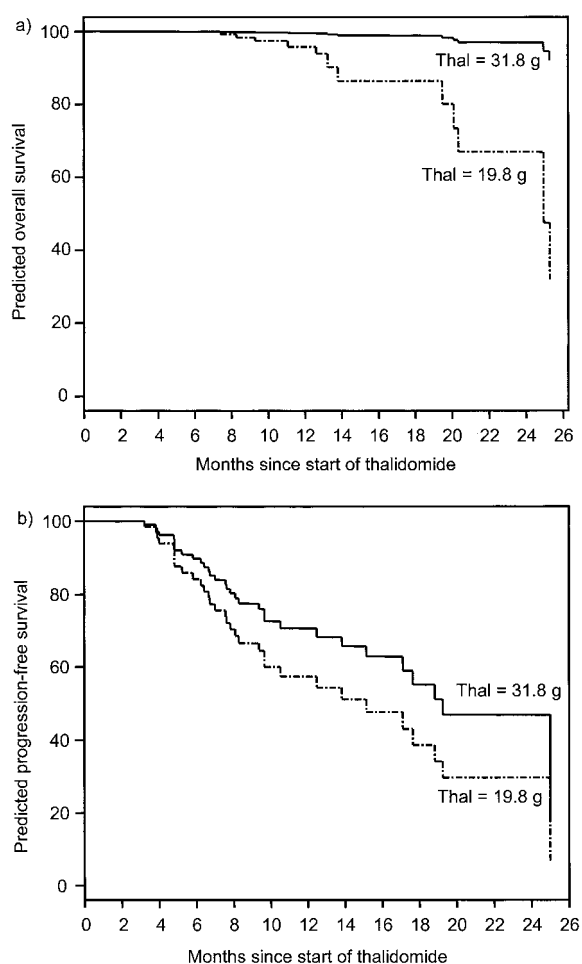


Fig. 3 Predicted OS (a) and PFS (b) for 69 PTs with relapsed MM during Thal therapy. All PTs received Thal therapy for at least 3 months. A Cox proportional hazards regression analysis was performed including age, β_2 -microglobulin, hemoglobin, albumin, C-reactive protein, and the cumulative Thal dosage within the first 3 months of treatment as possible prognostic factors. Predicted values were computed for a cumulative 3-month Thal dosage of 31.8 g and compared with a cumulative 3-month Thal dosage of 19.8 g, holding other factors of the model fixed at their median values. After 18 months of treatment, the PT group tolerating the maximum Thal dose of 400 mg daily (cumulative 3-month Thal dose of 31.8 g) had a 15–20% higher predicted PFS and OS as compared with PTs with a dose reduction from 400 to 200 mg after the first month of Thal therapy (cumulative 3-month Thal dose of 19.8 g).

that Thal acts directly by inducing apoptosis or G_1 growth arrest in MM cell lines and in PT MM cells in a dose-dependent manner. In addition, it has been shown that some of the immunomodulatory effects of Thal are also dose dependent, implying the inhibition of tumor necrosis factor α secretion by stimulated human monocytes (17). In an elderly prostate cancer patient population, the half-life time of Thal was shown to be dose related [6.52 ± 3.81 h at 200 mg/day and 18.25 ± 14.08 h at 1200 mg/day (18)]. Taking these laboratory and clinical findings together, MM PTs should be treated with dose-intensive Thal treatment schedules to obtain high response rates. Based on our experience, we recommend a Thal dosage of 400 mg daily for at

Table 4 Effect of the cumulative Thal dosage alone and in combination with parameters reflecting body size after 3 months of treatment^a

Parameter	Effect on PFS <i>P</i>	Effect on OS <i>P</i>
Thal alone	0.30	0.001
Thal/body mass index	0.53	0.01
Thal/body surface area	0.63	0.01
Thal/body weight	0.42	0.15
Thal/height	0.59	0.002

^a Each factor was added separately to the Cox proportional hazards regression models including age, β_2 -microglobulin, albumin, hemoglobin, and C-reactive protein.

least 3 months whenever the drug is tolerated. However, in previous studies, toxicities were related to the cumulative dose of Thal administered, and remissions of >30 months have been observed with Thal doses of only 50 mg daily (8, 9). Therefore, the question of the optimal dose-effect relationship with acceptable toxicity profile should be addressed in clinical Phase III trials. In addition, new treatment protocols combining Thal with cytotoxic agents might help to increase the response rate in MM and to reduce serious Thal-related toxicity. For example, we demonstrated recently the feasibility and efficacy of a combination of Thal, cyclophosphamide, etoposide, and dexamethasone in 56 MM PTs with poor prognosis, resulting in an objective response rate of 86% (15).

When Thal was used as a single agent in the treatment of refractory and relapsed MM, most adverse effects were mild or moderate (1). However, toxicities of >grade 2 were observed in 27% of our PTs and in 58% of PTs in the Barlogie *et al.* study (8). Because the median cumulative 3-month Thal dosage was 24% lower in the present study (31.8 g versus 42 g), the higher toxicity rate observed by Barlogie *et al.* (8) might be due, at least in part, to a more dose-intensive treatment schedule. Of note, only one PT presented with a grade 3 hematological toxicity in the current study. This observation suggests that Thal is an ideal agent to be used in myelosuppressive PTs as a single agent or in combination with dexamethasone. Although the addition of dexamethasone to Thal seems to increase the efficacy in MM (19), there was a report of a life-threatening toxic epidermal necrolysis in a MM PT (20). Hence, an adverse interaction between dexamethasone and Thal seems to be possible, and additional studies are needed on drug interactions.

As shown in the current study and by Barlogie *et al.* (8), there is a deep venous thrombosis rate between 2% and 4% when Thal is used as a single agent in MM PTs. Of importance, higher rates of up to 28% have been observed when Thal was given in combination with chemotherapy (15, 21). In particular, the Arkansas experience (21) shows an increased incidence of deep venous thrombosis when Thal is given in combination with anthracyclines. For this reason, we recommend prophylactic low molecular weight heparin in our ongoing Phase III trial comparing the efficacy of vincristine, doxorubicin, dexamethasone versus AD plus Thal as induction therapy for newly diagnosed MM PTs.

Interestingly, the effect on OS could not be improved when the cumulative 3-month Thal dosage was related to parameters reflecting body size. Like the dexamethasone dosage in the

widely used VAD regimen for treatment of MM (22), actual treatment schedules do not consider the body weight or height of each MM PT to determine the individual Thal dosage (8, 9, 16). In line with our results, previous reports on Thal pharmacokinetics show that the interindividual variability in distribution and elimination is low, suggesting that an adjustment of Thal dosage to parameters reflecting body size does not improve outcome after Thal treatment in MM in comparison with Thal alone irrespective to body mass parameters (18, 23). However, little is known about the active Thal metabolites and their interindividual variability in production *in vivo*. Therefore, future approaches should include pharmacogenetic studies to determine individual factors that predict response to Thal therapy at a genomic level (24).

In conclusion, we have shown that Thal has a dose-dependent effect on OS in relapsed MM, although the question of the minimal effective Thal dosage is still unresolved. Because toxicities seem to be related to the dose intensity of Thal, and some PTs remain in a stable remission for >30 months with Thal dosages as low as 50 mg daily (8, 9), further issues regarding pharmacokinetics, pharmacogenetics, dose intensity, and scheduling need to be studied in prospective trials.

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