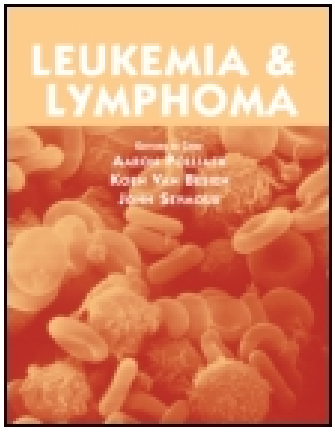

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A randomized trial with melphalan and prednisone versus melphalan and prednisone plus thalidomide in newly diagnosed multiple myeloma patients not eligible for autologous stem cell transplant

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A randomized trial with melphalan and prednisone versus melphalan and prednisone plus thalidomide in newly diagnosed multiple myeloma patients not eligible for autologous stem cell transplant

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Abstract

Several trials comparing the efficacy of standard melphalan and prednisone (MP) therapy with MP plus thalidomide (MPT) in elderly patients with multiple myeloma (MM) have been reported, with inconsistent results. The primary goal of our study was to evaluate the efficacy and toxicity of MP versus MPT in newly diagnosed patients with MM who were transplant-ineligible or over age 65. A total of 135 patients were enrolled. Either minimal response or better or partial response or better were more frequent with MPT treatment ($p = 0.001$). After a median follow-up of 30 months, median progression-free survival (PFS) and overall survival (OS) were 33 and 52 months for MPT versus 22 and 32 months for MP, respectively. The comparison showed a significant advantage for MPT versus MP in PFS ($p = 0.02$) and only a trend for OS ($p = 0.07$). Severe adverse events were observed more frequently with MPT. In conclusion, our results show an improved activity of MPT at a cost of increased toxicity. We believe that MPT can be considered one of the new standard of care for elderly or transplant-ineligible patients with MM.

Keywords: *Multiple myeloma, thalidomide, melphalan, prednisone, OS, PFS*

Introduction

In Italy, the incidence of multiple myeloma (MM) is approximately 4 per 100 000 persons per year [1]; at least half of newly diagnosed patients are over age 65. During the last decade, the survival of younger patients has increased due to the widespread use of autologous stem cell transplant (ASCT) and

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advancements in its application. However, survival has improved only modestly in patients who are ineligible for high-dose chemotherapy with stem cell support. Until recently, melphalan plus prednisone (MP) was the most commonly used therapy in these patients. The introduction of novel agents with activity in MM, such as thalidomide, bortezomib, and lenalidomide, has modified the therapeutic approach to newly diagnosed, relapsing, or refractory patients. Thalidomide is an immunomodulatory agent with demonstrated efficacy against MM [2]. Six randomized studies assessed the combination of MP plus thalidomide (MPT) in newly diagnosed patients ineligible for high-dose treatment [3–9]. However, these trials were variable in terms of inclusion criteria, patient characteristics, and treatment schedules. Further, although all studies reported an improvement in response rate with the addition of thalidomide, results were variable in terms of survival outcomes. Our trial began enrolling patients in 2005, when limited data were available, with the primary goal of evaluating the efficacy and toxicity of MP versus MPT in transplant ineligible or elderly untreated patients with MM.

Methods

Patient selection

Patients over age 65 years and younger patients who were ineligible for high-dose treatment with newly diagnosed stage II or III MM and Eastern Cooperative Oncology Group (ECOG) performance status of 3 or less were eligible. Exclusion criteria were primary amyloidosis, polyneuropathy, severe cardiac, hepatic, or pulmonary dysfunction, a diagnosis of human immunodeficiency virus (HIV), hepatitis C virus (HCV), or positive serum hepatitis B surface antigen (HBsAg), renal failure with dialysis dependency, history of other malignancy, female of childbearing age, and diagnosis of psychiatric disease. Patients were recruited from 10 hospitals in Italy from January 2005 to December 2008. The central ethics committee in Modena and the local ethics committee of each participating center approved the study. The trial was prepared according to the Declaration of Helsinki and all patients provided written informed consent. The trial was registered at www.clinicaltrial.gov, number NCT01274403.

Study design

The trial was designed as an open label, unblinded, multicenter, randomized phase II study. Patients were centrally randomized to receive either MP or MPT. The randomization was stratified according to ECOG performance status (0–1/2–3), stage (II/III), and age. The MP regimen consisted of 6–12 cycles of chemotherapy administered every 28 days. Melphalan (0.25 mg/kg) and prednisone (60 mg/m^2) were given orally for 4 days for a maximum of 48 weeks. The MPT regimen consisted of the same MP dosing schedule with the addition of thalidomide (Pharmion, Windsor, UK) at a dose of 100 mg per day continuously for a maximum of 48 weeks. At least six cycles of MP or MPT were planned (minimum of six and maximum of 12 cycles). In case of an ongoing response (less than complete response [CR]) after six cycles, treatment was continued for a maximum of a further six cycles and then response was reevaluated, i.e. treatment was continued until a plateau phase was reached. Concomitant treatment with bisphosphonates was recommended. From 2007, a maximum treatment period of 2 years was recommended in patients without active disease. No anticoagulant prophylaxis was planned. Transfusion of red blood cells (RBCs) and platelets and the administration of neutrophil growth factors or erythropoiesis-stimulating agents were permitted as required. Plasmapheresis as initial treatment and radiotherapy to localized lesions were also permitted. A randomized maintenance treatment with dexamethasone or dexamethasone plus thalidomide was planned. However, maintenance treatment was administered in only three centers to a total of 21 patients for a period of 1–5 months. Twelve and nine patients were treated with thalidomide plus dexamethasone or dexamethasone, respectively. Further, 13 patients received 3 or fewer months of treatment and eight patients five or fewer cycles.

Progression-free survival curves of patients who received maintenance treatment did not show differences with those of patients who did not. Thus, no further analysis was performed of this group.

Assessment

The response to treatment was monitored according to modified criteria of the European Group for Blood and Marrow Transplantation – International Bone Marrow Transplant Registry [10].

Briefly, CR was defined as the complete disappearance of M protein in serum and urine confirmed by immunofixation and bone marrow plasma cells less than 5%. Partial response (PR) was defined as at least 50% reduction of M protein in serum and a 90% decrease in urine. Minimal response (MR) was defined as a decrease in M protein of 25–49% in serum and of 50–89% in urine. No confirmation of response was needed for complete, partial, or minimal response. Progressive disease was defined as an increase in serum M protein of more than 25%

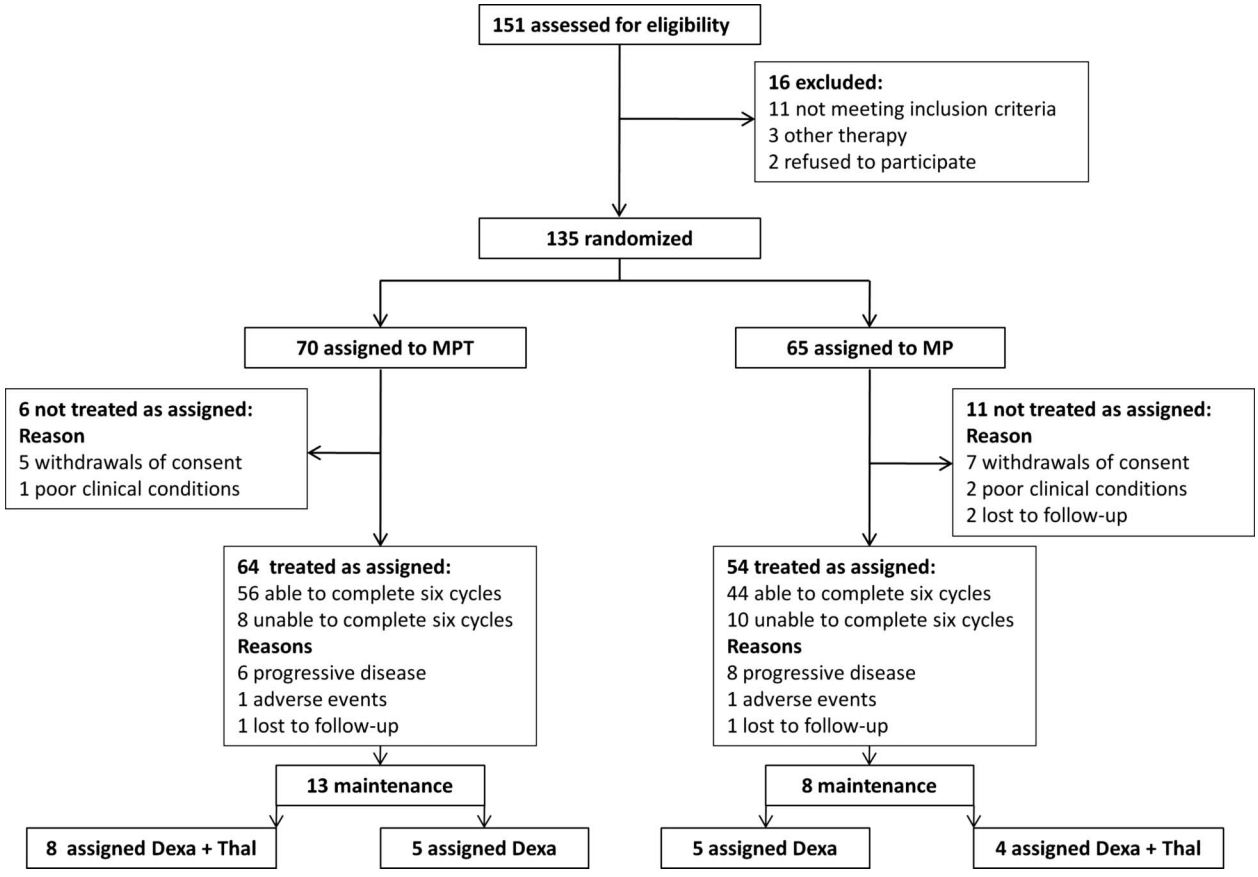

Figure 1. Trial profile.

and the development of new lesions. Patients not meeting the criteria for response or progressive disease were classified as having stable disease. The best response was defined as the highest amount of disease improvement achieved by a patient at any follow-up visit while on treatment.

Statistical analysis

Clinical parameters were registered prospectively at the time of each patient entry in the clinical trial. Overall survival (OS) was defined from the date of being randomly assigned to the date of last observation or death from any cause. Progression-free survival (PFS) was defined from the date of being randomly assigned to the date of disease progression, date of last observation, or death from any cause. Survival differences were analyzed using the Kaplan–Meier method [11]. Differences in baseline characteristics of patients in the different treatment groups were evaluated using the χ^2 test for categorical variables and Kruskal–Wallis rank test for variables in continuous form. Best response rates were compared between treatment groups using the χ^2 test. Comparison between survival curves was checked by means of Cox proportional hazards (PH) regression [12] in both univariate and multivariate analysis, and the effect size was expressed as a hazard ratio (HR) and its 95% confidence interval (95% CI). Age, β_2-microglobulin, and type of treatment were used as covariates. The proportional hazards assumption was checked by means of graphical analysis of Schoenfeld residuals [13]. All analyses were performed according to the intent-to-treat principle. Statistical analyses were performed using the Stata software package, version 10.1 [14].

Results

Between January 2005 and December 2008, 151 patients were assessed for eligibility and 16 were excluded. A total of 135 patients were enrolled, with 70 randomly assigned to receive oral MPT and 65 to receive MP. The median age was 77 years (range 66–89 years), with 61% of patients older than 75 years and 33% older than 80 years. A total of 17 patients in the two arms were not treated as assigned: 12 withdrew consent, three deteriorated clinically, and two were lost to follow-up. Thus, 64 patients received MPT and 54 received MP. Eight patients

in the MPT group and 10 in the MP group did not complete the assigned treatment (Figure 1). The patients were well balanced for baseline demographics and disease characteristics, except for disease stage (Table I). At the time of the analysis in October 2010 the median follow-up was 30 months.

Response rate

Table II reports treatment response rates. Minimal response or better was observed more frequently in the MPT group than in the MP group ($p = 0.001$). Also, excluding minimal response, the difference between MPT versus MP arm in terms of CR and PR remained statistically significant ($p = 0.001$) Stable disease was observed in 5% and 11% of patients in the MPT and MP groups, respectively ($p > 0.05$). Disease progression occurred in 8% and 32% of the MPT and MP groups, respectively ($p = 0.001$).

Survival

Median PFS was 33 months for the MPT group compared with 22 months for the MP arm ($p = 0.02$, Figure 2). Even in the very elderly patients (>75 years old) we observed an improvement in PFS with MPT ($p = 0.04$).

On multivariate analysis, MPT and age ≤75 years were good prognostic factors: the hazard ratio was 0.5 (95% CI 0.3–0.9) for MPT and 0.6 (95% CI 0.4–0.9) for age ≤75 years. OS was better in the MPT group compared to the MP group (52 vs. 32 months, respectively), but there was only a trend toward statistical significance ($p = 0.07$, Figure 3).

We did not find statistically significant differences when comparing patients younger versus older than 75 years of age. A multivariate Cox model was not statistically significant ($p = 0.19$, Cox model).

Table I. Patient demographic and clinical characteristics.

	Total patients, $n = 118$		
Characteristic	MP, $n = 54$ (100%)	MPT, $n = 64$ (100%)	p-Value
Sex			
Female	28 (52)	35 (55)	>0.05
Age (years)			
Median	79	76	
Range	68–88	66–89	
66–70	7 (13)	7 (11)	>0.05
71–75	12 (22)	20 (31)	
>75	35 (65)	37 (59)	
Durie and Salmon stage			
IIA–B	23 (42)	40 (62)	<0.05
IIIA–B	31 (58)	24 (38)	
ISS*			
I	12 (22)	22 (34)	>0.05
II	21 (39)	27 (42)	
III	16 (30)	14 (22)	
Missing	5 (9)	2 (3)	
Myeloma protein class			
IgA	13 (24)	12 (19)	>0.05
IgG	34 (63)	47 (73)	
Bence Jones protein	7 (13)	5 (8)	
ECOG performance status			
0–2	46 (85)	53 (83)	>0.05
3–4	5 (9)	8 (12)	
Missing	3 (6)	3 (5)	
β_2-Microglobulin (mg/dL)			
Median	4.8	4.8	>0.05
95% CI	2–9	2–9	

*Calculated in 94% of patients because in 6% albumin level was missing.

MP, melphalan and prednisone; MPT, melphalan, prednisone, and thalidomide; ISS; international staging system; IgA, immunoglobulin A; IgG, immunoglobulin G; ECOG; Eastern Cooperative Oncology Group; CI, confidence interval.

Table II. Response to treatment*.

	MP, $n = 54$ (100%)	MPT, $n = 64$ (100%)	p-Value
CR	4 (7)	13 (20)	0.047
PR	23 (43)	38 (59)	>0.05
MR	4 (7)	5 (8)	>0.05
SD	6 (11)	3 (5)	>0.05
PD	17 (32)	5 (8)	0.001

*CR + PR vs. MR + SD + PD, $p = 0.001$.

MP, melphalan and prednisone; MPT, melphalan, prednisone, and thalidomide; CR, complete response; PR, partial response; MR, minimal response; SD, stable disease; PD, progressive disease.

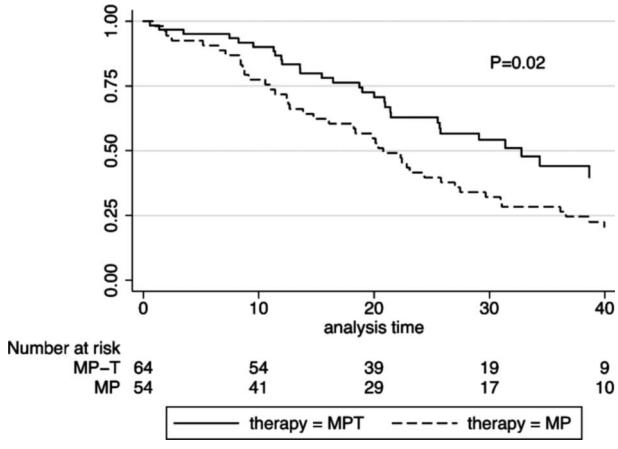

Figure 2. Progression-free survival by treatment. MPT, melphalan, prednisone, and thalidomide; MP, melphalan and prednisone.

Toxicity

Table III reports the safety profile evaluated by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0. Severe adverse events were observed more frequently in the MPT group. The most frequent events were neutropenia, constipation, nausea/vomiting, deep venous thrombosis, infection, and peripheral neuropathy. Treatment-related neutropenia caused a delay in subsequent cycle administration in 30% and 12% of patients in the MPT and MP groups, respectively.

Discussion

In this randomized trial, we found that the addition of thalidomide to MP in elderly patients with MM has superior activity against MM in comparison to MP alone in terms of both response rate and increased PFS. OS also improved with MPT, but the advantage fell just short of statistical significance. Adverse events were more frequent in the MPT group. In particular we observed a significant increase in neutropenia, deep venous thrombosis, infection, and peripheral neuropathy. Thus, our results show increased activity against MM at a cost of greater toxicity. Venous thromboemolism is now a well-known adverse effect of thalidomide treatment. However, in the period 2002–2006, none of the trials comparing MP with MPT initially used prophylaxis against deep venous thrombosis (DVT). Only the GIMEMA (Italian Group for Adult Hematologic Diseases) [3] and HOVON (Dutch-Belgian Hemato-Oncology Cooperative Group)-49 [7] trials were subsequently amended to include prophylaxis, and the rates of venous thromboembolism were reduced. The low incidence of DVT in the Nordic study [8] may be explained by the use of anti-thrombotic drugs in about 40% of patients. Now it is well known that the risk of venous thromboembolism can be reduced, following the recommendation for the prevention of immunomodulatory drug (IMiD)-induced DVT [15].

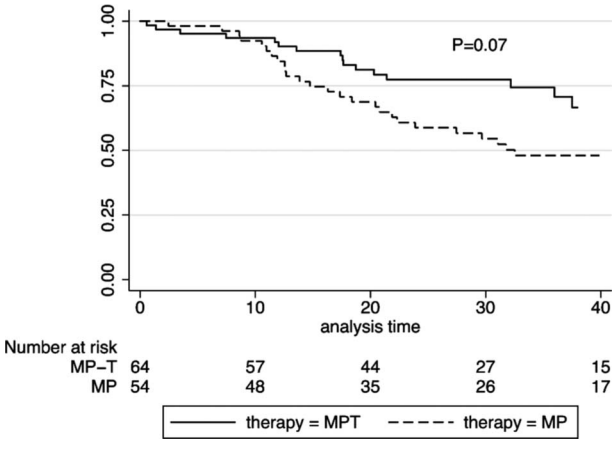

Figure 3. Overall survival by treatment. MPT, melphalan, prednisone, and thalidomide; MP, melphalan and prednisone.

Table III. Grade 3 and 4 adverse events evaluated by NCI CTCAE criteria.

	MPT, $n=64$		MP, $n=54$		
Adverse event	*n*	%	*n*	%	*p*-Value
Infection	6	9	1	2	<0.05
Neutropenia	18	28	7	13	<0.05
Deep venous thrombosis	7	11	0	0	<0.05
Peripheral neuropathy	4	6	0	0	<0.05
Renal dysfunction	0	0	2	4	<0.05
Constipation	11	17	3	6	<0.05
Nausea/vomiting	8	12	6	11	>0.05

NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; MPT, melphalan, prednisone, and thalidomide; MP, melphalan and prednisone.

The concurrent administration of melphalan and thalidomide enhanced myelosuppressive effects, and grade 3 or 4 neutropenia and infection were more common in the MPT arm, causing a delay in subsequent chemotherapy cycle administration in 30% of patients in the MPT group. Also the incidence of polyneuropathy was greater with MPT.

In the various trials, dose schedules of MP varied greatly. However, none of the studies was designed for evaluating the optimal dose of thalidomide, and it is difficult to draw conclusions about dose or duration and efficacy of thalidomide treatment. We decided to use a low dose of thalidomide for several reasons, including the age of the patients, duration of induction therapy until 12 months, and planned and subsequently not delivered maintenance treatment. The dose schedule of thalidomide is variable in the different trials: in the induction phase from 100 to 400 mg day, and in the maintenance phase from 50 to 200 mg day. Although six randomized trials [3–9] were performed, along with a well-done meta-analysis [15], the thalidomide dose corresponding to better efficacy and fewer side effects is still unknown. We would like to underline that in our trial also, a dose as low as 100 mg/day was enough to induce beneficial effects.

Prior to the present study, several randomized trials investigated the effect of adding thalidomide to classical MP, and reported inconsistent results. All previous studies reported a significant increase in response rate with the addition of thalidomide. However, results concerning impact on survival outcome are contradictory (Table IV). In all studies,

Table IV. Results of seven randomized trials comparing MPT versus MP.

Study [ref.]	Country	Response	OS	PFS	EFS
Palumbo, 2006 [3]	Italy	$p < 0.05$*	NS	ND	$p < 0.05$
Facon, 2007 [4]	France	$p < 0.05$	$p < 0.05$	$p < 0.05$	ND
Palumbo, 2008, update [5]	Italy	$p < 0.05$	NS	$p < 0.05$	ND
Hulin, 2009 [6]	France, Belgium	$p < 0.05$	$p < 0.05$	$p < 0.05$	ND
Wijermans, 2010 [7]	Netherlands	$p < 0.05$	$p = 0.05$	$p < 0.05$	$p < 0.05$
Waage, 2010 [8]	Sweden, Norway, Denmark, UK	$p < 0.05$	NS	NS	ND
Beksac, 2011 [9]	Turkey	$p < 0.05$	NS	NS	ND
Sacchi, 2011	Italy	$p < 0.05$	NS	$p < 0.05$	ND

*p-Value < 0.05 indicates a statistically significant difference in favor of MPT vs. MP arm.
MPT, melphalan, prednisone, and thalidomide; MP, melphalan and prednisone; OS, overall survival; EFS, event-free survival; PFS, progression-free survival; NS, not statistically significant; ND, not done.

with the exception of the Nordic [8] and Turkish trials [9], significant improvement in PFS or event-free survival (EFS) was observed, while improvement in OS was reported only in the two French and the Dutch studies [4,6,7]. There are several differences among studies that may account for the variability in results. The most important aspects regard inclusion criteria, percent of patients with poor or good performance status, median age, induction treatment duration, maintenance treatment, and MPT dose schedule. A recently published meta-analysis [16] reports that the addition of thalidomide to MP significantly improves the response rate and PFS, with a trend toward improvement in OS. This conclusion is similar to that reported in a recently presented abstract [17].

However, lacking direct comparison between MPT and MP plus bortezomib, physicians are not sure what treatment they should choose in the case of newly diagnosed patients with MM who are not eligible for ASCT. National Comprehensive Cancer Network Guidelines [18] recommend each of these treatments. In conclusion, we believe that MPT can be considered one of the new standards of care for the treatment of patients with MM over age 65 years and for younger patients who are transplant-ineligible; overall, this represents more than 50% of newly diagnosed patients.

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