VOLUME 28 · NUMBER 19 · JULY 1 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase III Study of the Value of Thalidomide Added to Melphalan Plus Prednisone in Elderly Patients With Newly Diagnosed Multiple Myeloma: The HOVON 49 Study

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Submitted November 25, 2009; accepted April 8, 2010; published online ahead of print at www.jco.org on June 1, 2010.

Written on behalf of the Dutch-Belgium Cooperative Group HOVON.

Supported in part by the Dutch Cancer Foundation, Koningin Wilhelmina Fonds.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/10/2819-3160/$20.00

DOI: 10.1200/JCO.2009.26.1610

ABSTRACT

Purpose
For several decades, the treatment of elderly patients with multiple myeloma (MM) has consisted of melphalan and prednisone (MP). The Dutch-Belgium Hemato-Oncology Cooperative Group (HOVON) investigated the efficacy of thalidomide added to MP (MP-T) in a randomized phase III trial. The objective of this study was to investigate the efficacy, toxicity, and effects on quality of life of MP-T.

Patients and Methods
A randomized phase III trial compared standard MP with MP-T (thalidomide 200 mg/d) in newly diagnosed patients with multiple myeloma older than age 65 years. Maintenance therapy with thalidomide 50 mg/d was administered to patients after MP-T until relapse. The primary end point was event-free survival (EFS); response rate, overall survival (OS), and progression-free survival (PFS) were secondary end points.

Results
An intent-to-treat analysis of 333 evaluable patients showed significantly higher response rates in MP-T–treated patients compared with MP-treated patients a response (≥ partial response: 66% *v* 45%, respectively; $P < .001$; and ≥ very good partial response [VGPR]: 27% *v* 10%, respectively; $P < .001$). EFS was 13 months with MP-T versus 9 months with MP ($P < .001$). OS was 40 months with MP-T versus 31 months with MP ($P = .05$).

Conclusion
This study demonstrates that thalidomide improves the response rate and VGPR in elderly patients with newly diagnosed MM. MP-T also results in a better EFS, PFS, and OS.

J Clin Oncol 28:3160-3166. © 2010 by American Society of Clinical Oncology

INTRODUCTION

For several decades, melphalan plus prednisone (MP) was the standard treatment for elderly patients with multiple myeloma (MM). Several chemotherapeutic combinations have been tried to improve the treatment outcome, but in a meta-analysis, it was shown that no benefit on overall survival (OS) was obtained.[1] It also became clear that the addition of interferon alfa to MP resulted in a small improvement in event-free survival (EFS); however, no improvement was seen in OS.[2] Singhal et al[3] described for the first time a beneficial effect of thalidomide in refractory MM patients. Several phase I and II studies confirmed the positive effect of thalidomide and showed that better response rates were obtained if thalidomide was combined with dexamethasone.[4-6]

The Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON) started a phase III study to compare the standard MP therapy with MP plus thalidomide (MP-T) in newly diagnosed elderly patients with MM. Before accrual was completed, publications of two trials showed a beneficial effect of the addition of thalidomide to MP treatment in elderly patients, although at the time of publication, these two studies were not conclusive with respect to OS, with a survival benefit in the Intergroupe Francophone du Myélome (IFM) study that was not confirmed in the Italian study.[7,8] Based on recommendations of the data safety monitoring board, it was decided to stop the HOVON study at an accrual of 344 of the estimated 420 patients because the required number of events had been reached.

PATIENTS AND METHODS

Study Design

The trial was designed as an open-label, multicenter, phase III randomized study in which standard MP was compared with MP-T in patients with previously untreated MM older than age 65 years. The primary objective was to measure the effect of the addition of thalidomide on EFS. Secondary end points were response, OS, and progression-free survival (PFS). The safety and toxicity of MP-T were also assessed including quality of life (QOL).

The central ethics committee and the local ethics committee of each participating hospital approved the study. The study was performed according to the Declaration of Helsinki, and all patients gave their written informed consent. The trial was registered under ISRCTN 90692740.

Patient Selection

Patients older than age 65 years with a newly diagnosed stage IB, II, or III MM, a WHO performance status of 0 to 3, and a measurable tumor parameter were eligible. Exclusion criteria were the presence of amyloid light-chain amyloidosis; polyneuropathy; severe cardiac, pulmonary, and hepatic dysfunction; renal failure with dependency on dialysis; uncontrolled infection of any kind or HIV positivity; and other malignancies. Pretreatment with chemotherapy or corticosteroids was not allowed.

Treatment Schedule

Melphalan 0.25 mg/kg and prednisone 1 mg/kg were administered daily for 5 days every 4 weeks. In MP-T, thalidomide 200 mg/d was administered continuously until 4 weeks after the last MP-T cycle. Eight cycles of MP or MP-T were planned. In case of an ongoing response, MP or MP-T cycles were continued until a plateau phase was reached. Patients who completed the planned MP-T cycles received maintenance therapy with thalidomide 50 mg/d until progression. Patients in the MP arm received no maintenance. After disease progression or no response, salvage therapy was given according the physician's choice.

Treatment with bisphosphonates was recommended using either pamidronate or clodronate. From 2007, a maximum treatment period of 2 years was recommended in patients without active disease.

At the start of the trial, no guidelines for thrombosis prophylaxis were given. From 2005, low molecular weight heparin (nadroparin 2,850 U anti-Xa or 5,700 U anti-Xa in case of weight > 90 kg) was recommended as standard prophylaxis during MP-T, whereas during maintenance, low-dose aspirin was advised.[9] It is unknown how many patients received thrombosis prophylaxis.

Study End Points

Response analysis was performed after three, six, and eight cycles; after the last MP/MP-T cycle; and yearly during maintenance or follow-up. Responses were scored according to the European Bone Marrow Transplantation Group criteria.[10]

Complete response (CR) was defined as complete disappearance of M protein confirmed by immunofixation and bone marrow plasma cells less than 5%. Very good partial response (VGPR) was defined as a decrease of more than 90% of the M protein. Partial response (PR) was defined as a decrease of the M protein of more than 50% but less than 90%. Minimal response was defined as a decrease of the M protein of more than 25% but less than 50%. Progressive disease required an increase of more than 25% of serum M protein, with an absolute increase of more than 5 g/L or more than 25% of 24-hour urine M protein; development of new lesions; or an increase of more than 25% in pre-existing bone lesions or soft tissue plasmacytomas. A plateau phase was reached if stable M proteins were present for at least 3 months. Toxicity of the two regimens was assessed by laboratory evaluation, physical examination, vital signs, and adverse events assessments. Adverse events were scored using the National Cancer Institute (NCI) Common Toxicity Criteria (CTC), version 2.0.

EFS was defined as the time from registration to induction failure, death, progression, or relapse, whichever occurred first. OS was measured from time of registration. Patients still alive or lost to follow-up were censored at the date they were last known to be alive. PFS was measured from the time of achievement of PR or CR to the date of relapse, disease progression, or death from any cause.

QOL Analysis

The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 is a multidimensional, cancer-specific QOL questionnaire developed by the EORTC Study Group on Quality of Life for use in international clinical trial settings. The EORTC Quality of Life Questionnaire MY24 was used to measure specific aspects that are relevant for the QOL in patients with MM.[11]

Table 1. Patient Demographic and Clinical Characteristics

Characteristic	No. of Patients MP (n = 168)	MP-T (n = 165)	P
Sex			.685
Female	76	71	
Male	92	94	
Age, years			
Median	73	72	
Range	65-84	65-87	
66-70	58	68	.300
71-75	58	45	
> 75	52	52	
WHO grade			.387
0	54	67	
1	81	73	
2	25	20	
3	8	5	
Stage			.860
IB	0	1	
IIA	44	38	
IIB	1	2	
IIIA	107	107	
IIIB	16	17	
ISS stage			.503
I	39	44	
II	39	42	
III	29	32	
Unknown	61	47	
Heavy chain			.918
IgA	49	50	
IgG	103	97	
IgD	0	1	
LCD	16	17	
M protein light chain			.183
κ	110	97	
λ	57	68	
Unknown	1	0	
Radiographic skeleton survey			.570
No lesions	49	46	
Single lesion	8	13	
2 lesions	10	5	
3+ lesions	97	93	
Unknown	4	8	
β_2-microglobulin, mg/L			.596
Median	4.0	4.0	
95% CI	1.9-14.1	1.5-11.1	
Albumin level, g/L			.551
Median	34	34	
95% CI	22-24	24-44	

Abbreviations: MP, melphalan and prednisone; MP-T, melphalan, prednisone, and thalidomide; ISS, International Staging System; IgA, immunoglobulin A; IgG, immunoglobulin G; IgD, immunoglobulin D; LCD, light-chain disease.

Statistical Analyses

The sample size estimation was based on EFS as the primary end point. A relative hazard rate of 0.7 for the MP-T arm corresponded with an increase in EFS from 60% to 70% at 1 year and from 15% to 27% at 5 years. For the detection of this difference with an $\alpha = .05$ (two-sided) and a power of 80%, 252 events were required. This number of events might be expected after recruitment of 420 patients in 4.5 years and an additional follow-up time after inclusion of the last patient of 1 year.

Differences in response rates were tested using a χ^2 test for differences in proportions. A log-rank test was used to test the differences in EFS, OS, and PFS by random assignment arm. Multivariate Cox regression analysis was used to adjust the effect of random assignment on EFS, OS, and PFS for the influence of other prognostic factors. Random assignment was performed by the HOVON data center. All analyses were performed according to the intent-to-treat principle.

RESULTS

Patient Accrual

The accrual of patients started in September 2002. In July 2007, the data safety monitoring board stopped the trial when 344 patients had been included based on two publications that indicated a superior effect of MP-T compared with MP alone.[7,8] Eleven patients were excluded because they did not comply with the entry criteria (five had nonsecreting MM, one had no MM, one had stage IA MM, one had other malignancy, one provided no informed consent, and two were not evaluable).

Patients and Treatment

Three hundred thirty-three patients were analyzed (186 men and 147 women; median age, 72 years; range, 65 to 87 years). Thirty percent of patients were ≥ 75 years old. The patients were well balanced for age, International Staging System stage, disease characteristics, and WHO performance status (Table 1). One hundred sixty-eight patients received 1,011 cycles of MP, and 165 patients received 970 cycles of MP-T; in the both arms, the median and mean number of cycles was four cycles and six cycles, respectively. The median follow-up time at the date of analysis was 39 months (Fig 1).

Response Rate

MP-T resulted in a significantly better response rate (CR+VGPR+PR) on protocol treatment than MP (66% *v* 45%, respectively; $P < .001$). CR was relatively low because immunofixation had not been mandatorily performed. After eight cycles, CR+VGPR was 23% with MP-T versus 8% with MP ($P < .001$). No effect of age on the difference by arm was observed, with a response rate in patients ≥ 75 years old of 66% in the MP-T arm and 44% in the MP arm (CR+VGPR of 23% and 13%, respectively). The number of nonresponders or patients with progressive disease was 55% with MP and 34% with MP-T ($P < .001$). Figure 2 shows the time to response for overall response (Fig 2A) and VGPR+CR (Fig 2B). After three cycles of MP-T, 58% of patients had achieved at least PR compared with 32% of patients on MP ($P < .001$).

Prolonged Treatment, Maintenance, and Second-Line Therapy

Nineteen patients on MP and 18 patients on MP-T received more than eight cycles until reaching a plateau level of M protein. This ongoing treatment led to a small increase from PR to VGPR of 2% in both arms.

Sixty-five (88%) of 74 eligible MP-T–treated patients received thalidomide as maintenance, with a median duration of 255 days (5% to 95% range, 43 to 1,094 days). Thalidomide-induced polyneuropathy (TiPN) was the main reason not to give or to stop maintenance

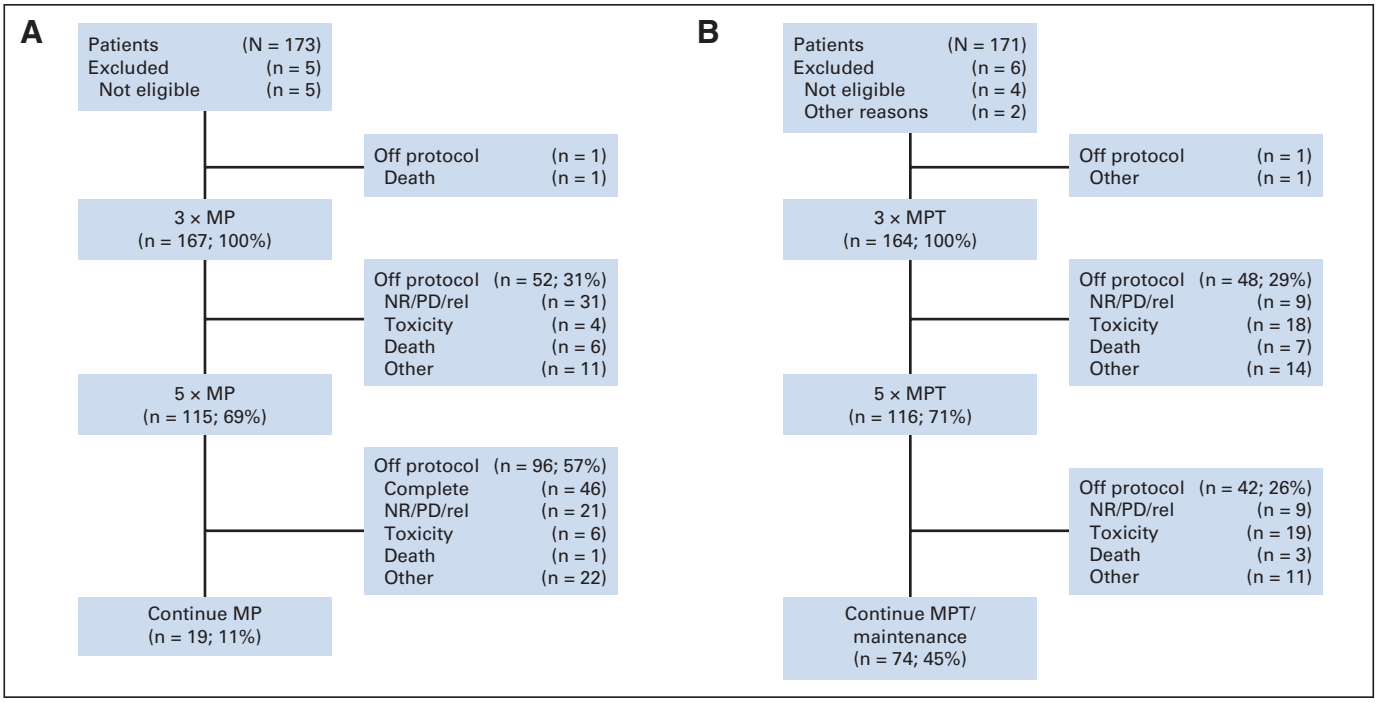

Fig 1. CONSORT diagram. MPT, melphalan, prednisone, and thalidomide; NR, no response; PD, progressive disease; rel, relapse; MP, melphalan and prednisone.

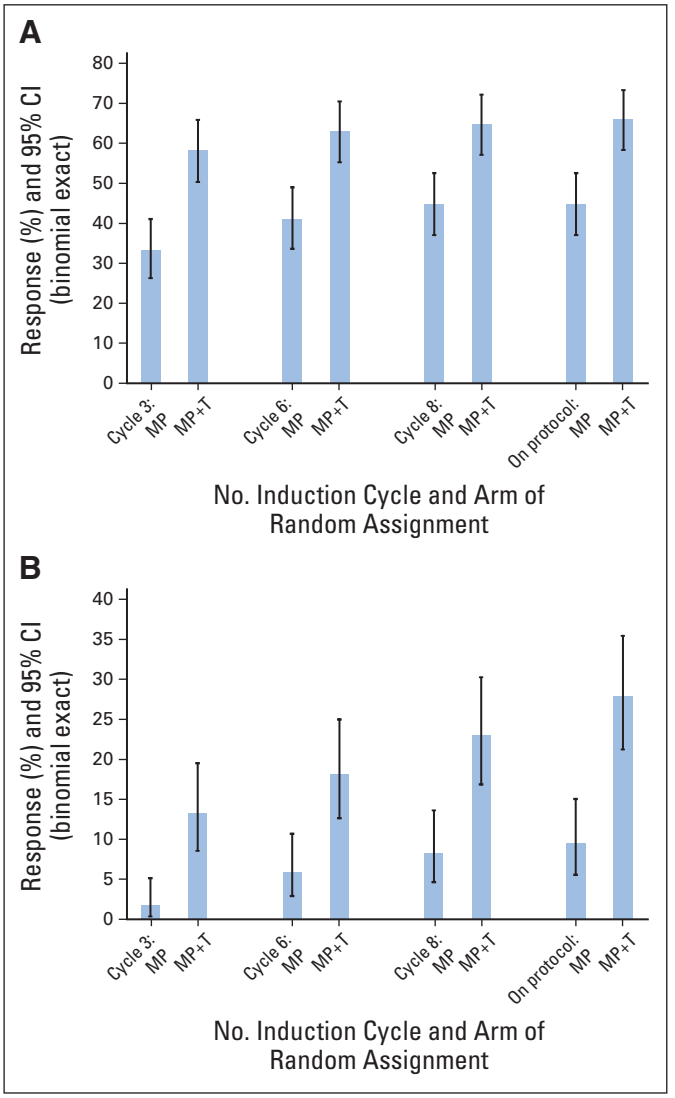

Fig 2. Time to response. MP, melphalan and prednisone; MP+T, melphalan, prednisone, and thalidomide. (A) CR + VGPR + PR; (B) CR + VGPR. CR, complete response; VGPR, very good partial response; PR, partial response.

therapy. During maintenance, an increase of CR+VGPR from 23% to 28% was observed.

Induction failure or disease progression during protocol treatment was observed in 52 patients in the MP arm and 18 patients in the MPT arm. The exact salvage treatment given because of progressive disease is not known, but a substantial number of patients (96 of 120 patients) from the MP arm received thalidomide as second-line therapy.

Survival

The median EFS was 9 months with MP and 13 months with MP-T ($P < .001$; Fig 3). The 2-year EFS was significantly better with MP-T than MP (29% *v* 10%, respectively; $P < .01$).

Median PFS from CR/PR was 15 months for MP-T compared with 11 months for MP ($P < .002$; Fig 3). The difference in PFS at 2 years was 34% with MP-T and 14% with MP. PFS from time of registration was also significantly better in patients treated with MP-T versus MP (33% *v* 21%, respectively; $P < .05$).

OS of patients treated with MP-T was significantly better than the OS of those treated with MP (40 *v* 31 months, respectively; $P = .05$). The 2- and 4-year OS rates were 67% and 43%, respectively, for MP-T compared with 61% and 30%, respectively, for MP. The multivariate Cox regression analysis of the most significant variables for response, EFS, PFS, and OS is shown in Table 2.

Even in the elderly ($\geq$ 75 years old), we observed an improvement in EFS ($P < .003$), although the median EFS was shorter (6 months for MP and 10 months for MP-T). In addition, the PFS was improved ($P = .03$) but not the OS (Fig 3).

In the multivariate analysis, WHO grade 2 or 3 appeared to be the strongest prognostic factor for OS, whereas MP versus MP-T was not significant. Therefore, we determined whether a different impact on OS with MP-T was present according to WHO grade. The multivariate analysis was extended with terms for interaction between arm of random assignment (MP-T *v* MP) and WHO grade. For WHO grade 1, the hazard ratio was 0.756, and for WHO grade 2 or 3, the hazard ratio was 1.536 (P for the two added terms of interaction = .069). Hence, the data indicate that an unfavorable clinical condition at baseline may be associated with the absence of a favorable effect of thalidomide on OS.

Toxicity

Treatment discontinuation as a result of toxicity in the MP arm was rather low (Fig 1). Neutropenia-related infection was probably the main reason, but only four of the 17 early deaths were related to an infection. MP-T was associated with a higher rate of toxicity. Treatment-related adverse effects of WHO grade 2 or higher occurred in 60% of MP-treated patients compared with 87% of MP-T–treated patients (Table 3). The higher rate of toxicity with MP-T was primarily due to TiPN, with NCI CTC grade 3 or 4 neuropathy being observed in 23% of patients. During maintenance, grade $\geq$ 2 TiPN was observed in 54% of patients. Venous thrombotic events occurred in 10% of MP-T–treated patients compared with only 1% of MP-treated patients. Treatment-related adverse events were the reason for going off study for 11 patients in the MP arm and 62 patients in the MP-T arm.

Given the relatively high dose of melphalan in this trial, dose reductions were required in 70% of patients, with no difference between MP and MP-T arms. One third of the patients treated with MP-T needed dose reductions of thalidomide (27%, 35%, and 34% at 3, 6, and 8 months of treatment, respectively). Table 4 lists the number of patients still in the protocol at the different time points and the number of patients who needed dose reductions for the different drugs.

Cytogenetics

Cytogenetic analysis using conventional karyotype banding techniques was successfully performed in 94 and 88 patients in the MP and MP-T arms, respectively. In patients with a complete or partial deletion of chromosome 13 (n = 33), no effect on response, EFS, PFS, or OS was observed in either treatment arm.

QOL

Two hundred eighty-five of 333 eligible patients participated in the QOL study. For most QOL subscales, a trend for improvement was observed during the treatment. There were no subscales indicating an unfavorable or favorable influence of thalidomide. The details of the QOL study will be presented separately.

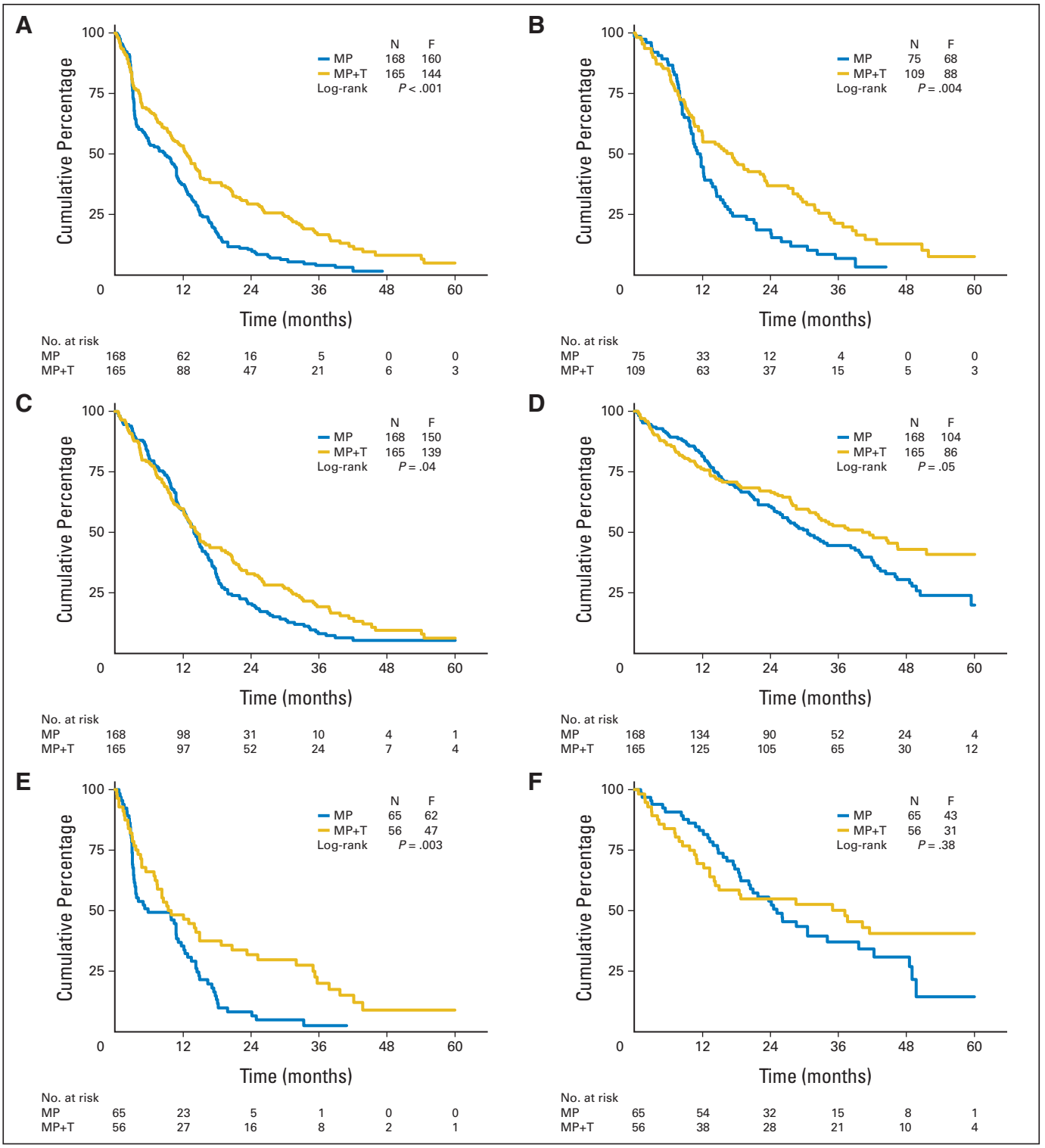

Fig 3. Kaplan-Meier survival curves. (A) Event-free survival (EFS). (B) Progression-free survival (PFS) from partial response (PR) or complete response (CR). (C) PFS from registration. (D) Overall survival (OS). (E) EFS in patients ≥ 75 years old. (F) OS in patients ≥ 75 years old. MP, melphalan and prednisone; MP+T, melphalan, prednisone, and thalidomide.

DISCUSSION

Recently, three trials showed an improved response rate with MP-T.[7,8,12] Another trial from the Nordic group reported relatively high rates of early toxicity with MP-T and moderate gains in response.[13] This HOVON trial confirms the superior effect of MP-T over MP on response rate. In addition, the time to response and quality of the response are significantly better because more patients achieve a

Table 2. Multivariate Regression Analysis

Outcome and Variable	HR	95% CI	*P*
Response rate			
Age	1.00	0.95 to 1.05	.97
WHO grade 1	0.71	0.43 to 1.60	.19
WHO grade 2/3	0.83	0.43 to 1.60	.57
M protein IgA	1.54	0.92 to 2.59	.1
M protein IgG	0.27	0.12 to 0.64	.0027
MP *v* MP-T	2.45	1.54 to 3.91	< .001
EFS			
Age	1.01	0.98 to 1.03	.57
WHO grade 1	1.16	0.90 to 1.51	.25
WHO grade 2/3	1.64	1.18 to 2.29	.004
M protein IgA	1.07	0.83 to 1.39	.59
M protein IgG	1.61	1.08 to 2.39	.02
MP *v* MP-T	0.65	0.61 to 1.00	< .001
PFS from CR/PR			
Age	1.00	0.97 to 1.03	.92
WHO grade 1	1.11	0.80 to 1.53	.54
WHO grade 2/3	1.78	1.17 to 2.72	.008
M protein IgA	1.49	1.10 to 2.02	.02
M protein IgG	1.11	0.57 to 2.17	.7
MP *v* MP-T	0.65	0.49 to 0.88	.006
OS			
Age	1.04	1.00 to 1.07	.04
WHO grade 1	1.56	1.12 to 2.19	.009
WHO grade 2/3	2.31	1.51 to 3.52	< .001
M protein IgA	1.33	0.96 to 1.85	.09
M protein IgG	1.57	0.99 to 2.50	.055
MP *v* MP-T	0.82	0.61 to 1.10	.19

Abbreviations: IgA, immunoglobulin A; IgG, immunoglobulin G; MP, melphalan and prednisone; MP-T, melphalan, prednisone, and thalidomide; EFS, event-free survival; PFS, progression-free survival; CR, complete response; PR, partial response; OS, overall survival.

VGPR or better with MP-T. MP-T also results in a longer EFS and PFS. In addition, a significant effect on OS has been observed at a follow-up time of 39 months. The response rate of this trial is comparable with the other MP-T versus MP trials, with rates ranging from 42% in the Nordic trial to 76% in the Italian and French trials.

As in the Italian and both French trials, we observed a superior EFS and PFS with MP-T. The results on OS differ among the studies.

Table 3. Adverse Events by NCI CTC

Adverse Event	% of Patients			
	MP		MP-T	
	Grade 2	Grade 3 or 4	Grade 2	Grade 3 or 4
Any toxicity	31	29	37	50
Neurologic	8	4	24	23
GI	16	7	24	5
Pain	7	8	11	4
Lung	10	3	14	3
Thrombosis	1	0	7	3
Infections	15	18	7	28

Abbreviations: NCI CTC, National Cancer Institute Common Toxicity Criteria; MP, melphalan and prednisone; MP-T, melphalan, prednisone, and thalidomide.

Table 4. Compliance

Cycle	No. of Patients on Protocol		% of Patients Who Received Planned Therapy on Time	
	MP	MP-T	MP	MP-T
Start of cycle 3	149	131		
Melphalan			38	48
Prednisone			55	62
Thalidomide			—	56
Start of cycle 6	98	97		
Melphalan			31	28
Prednisone			52	54
Thalidomide			—	44
Start of cycle 8	75	77		
Melphalan			28	22
Prednisone			59	61
Thalidomide			—	36

Abbreviations: MP, melphalan and prednisone; MP-T, melphalan, prednisone, and thalidomide.

The OS of 40 months with MP-T is comparable with the results of the French and Italian trials. However, a significant difference between MP-T and MP has only been observed in both IFM trials and this HOVON trial.[8,12] In the Italian study, the better response rate and EFS with MP-T did not lead to an OS benefit, even in an updated analysis.[14]

Comparing the response and survival data of the different studies is difficult because of the different dosing schedules of MP and MP-T. The melphalan dose in the HOVON study was higher than in any other trial. However, the differences in EFS and OS cannot easily be explained by the dosing of either melphalan or thalidomide. These drugs were given at a lower dose in one IFM study and in the Nordic study, with a survival advantage seen in the IFM trial only.[7,13] In the IFM study, in patients older than age 75 years, significantly lower doses of MP-T were given; however, a beneficial effect of thalidomide on OS was still observed.[13] The HOVON study also shows an improvement in response rate and EFS in patients ≥ 75 years old. However, the multivariate analysis with terms for interaction between arm and WHO status at entry indicated the absence of a favorable effect of thalidomide among patients with an unfavorable clinical condition at baseline.

In the Italian study, the thalidomide dose was relatively low, although maintenance with thalidomide was allowed.[7] A trial in younger patients treated with high-dose therapy showed improvement in EFS and a late effect on OS in only certain cytogenetic subgroups with the use of thalidomide.[15] More recently, no effect of thalidomide on OS was observed in the HOVON 50 trial.[16]

MP-T may be superior to thalidomide plus dexamethasone because Ludwig et al[17] found this combination to be inferior to MP regarding OS and toxicity. Whether MP-T is superior to the combination of cyclophosphamide, thalidomide, and dexamethasone, which did show promising activity in patients with relapsed disease, remains to be studied.[18]

In our study, the dose of melphalan was higher than in other studies. This might explain the high incidence of myelotoxicity in both arms. Thalidomide added significant neurotoxicity as the most significant adverse effect. GI adverse effects that may be related to intestinal

neuropathy were the second most important complication. Although thalidomide induced significant toxicity in MP-T–treated patients, it did not result in a reduction of the number of MP-T cycles that could be given when compared with the MP group. This toxicity also did not lead to a significant difference in dose reduction or affect QOL.

At the start of the study, no guidelines were given for thrombosis prophylaxis. Later, low-dose heparin was recommended. We do not have data on how many patients received prophylactic therapy, but a low incidence of NCI CTC grade 3 or 4 thrombosis was observed.

An open question is whether there are subpopulations of patients who benefit from thalidomide and those who experience only the adverse effects. From the different cytogenetic subgroups that we analyzed, no specific effect of 13q deletions was observed, although only 33 patients had this abnormality.

Maintenance therapy may have a favorable effect on outcome because we observed a further improvement of the quality of the response during maintenance. Two other studies have shown that maintenance or consolidation treatment when given to younger patients after intensive chemotherapy has a positive effect on OS.[19,20] In MP-T trials, the role of maintenance therapy remains unclear because, of the three trials with OS benefit, only the HOVON trial included maintenance treatment. Benefit of this maintenance treatment was seen, but a substantial number of patients experienced TiPN and had to stop maintenance treatment. As such, the role of maintenance treatment using other novel agents is still under investigation. We conclude that MP-T is an effective regimen for older patients with newly diagnosed MM with a clear benefit on survival.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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REFERENCES

1. Myeloma Trialists' Collaborative Group: Combination chemotherapy versus melphalan plus prednisone as treatment for multiple myeloma: An overview of 6,633 patients from 27 randomized trials. J Clin Oncol 12:3832-3842, 1998
2. Myeloma Trialists' Collaborative Group: Interferon as therapy for multiple myeloma: An individual patient data overview of 24 randomized trials and 4012 patients. Br J Haematol 113:1020-1034, 2001
3. Singhal S, Mehta J, Desikan R, et al: Antitumor activity of thalidomide in refractory multiple myeloma. N Engl J Med 341:1565-1571, 1999
4. Rajkumar SV, Blood E, Vesole D, et al: Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: A clinical trial coordinated by the Eastern Cooperative Oncology Group. J Clin Oncol 24:431-436, 2006
5. Richardson P, Anderson K: Thalidomide and dexamethasone: A new standard of care for initial therapy in multiple myeloma. J Clin Oncol 24:334-336, 2006
6. Rajkumar SV, Gertz MA, Lacy MQ, et al: Thalidomide as initial therapy for early-stage myeloma. Leukemia 17:775-779, 2003
7. Palumbo A, Bringhen S, Caravita T, et al: Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: Randomised controlled trial. Lancet 367:825-831, 2006
8. Facon T, Mary JY, Hulin C, et al: Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): A randomised trial. Lancet 370:1209-1218, 2007
9. Minnema MC, Breitkreutz I, Auwerda JJ, et al: Prevention of venous thromboembolism with low molecular-weight heparin in patients with multiple myeloma treated with thalidomide and chemotherapy. Leukemia 18:2044-2046, 2004
10. Bladé J, Samson D, Reece D, et al: Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. Br J Haematol 102:1115-1123, 1998
11. Sprangers MA, Cull A, Groenvold M, et al: The European Organization for Research and Treatment of Cancer approach to developing questionnaire modules: An update and overview. EORTC Quality of Life Study Group. Qual Life Res 7:291-300, 1998
12. Hulin C, Facon T, Rodon P, et al: Efficacy of melphalan and prednisone plus thalidomide in patients older than 75 years with newly diagnosed multiple myeloma: IFM 01/01 trial. J Clin Oncol 27:3664-3670, 2009
13. Waage A, Gimsing P, Juliusson G, et al: Melphalan-prednisone-thalidomide to newly diagnosed patients with multiple myeloma: A placebo controlled randomised phase 3 trial. Blood 110:32a, 2007 (abstr)
14. Palumbo A, Bringhen S, Liberati AM, et al: Oral melphalan, prednisone, and thalidomide in elderly patients with multiple myeloma: Updated results of a randomized controlled trial. Blood 112:3107-3114, 2008
15. Barlogie B, Pineda-Roman M, van Rhee F, et al: Thalidomide arm of Total Therapy 2 improves complete remission duration and survival in myeloma patients with metaphase cytogenetic abnormalities. Blood 112:3115-3121, 2008
16. Lokhorst HM, van der Holt B, Zweegman S, et al: A randomized phase III study on the effect of thalidomide combined with Adriamycin, dexamethasone and high-dose melphalan followed by thalidomide maintenance in patients with multiple myeloma. Blood 115:1113-1120, 2010
17. Ludwig H, Hajek R, Tóthová E, et al: Thalidomide-dexamethasone compared with melphalan-prednisolone in elderly patients with multiple myeloma. Blood 113:3435-3442, 2009
18. Roussou M, Anagnostopoulos A, Kastritis E, et al: Pulsed cyclophosphamide, thalidomide and dexamethasone regimen for previously treated patients with multiple myeloma: Long term follow up and disease control after subsequent treatments. Leuk Lymphoma 48:754-758, 2007
19. Attal M, Harousseau JL, Leyvraz S, et al: Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. Blood 108:3289-3294, 2006
20. Spencer A, Prince HM, Roberts AW, et al: Consolidation therapy with low-dose thalidomide and prednisolone prolongs the survival of multiple myeloma patients undergoing a single autologous stem-cell transplantation procedure. J Clin Oncol 27:1788-1793, 2009