Oral melphalan, prednisone, and thalidomide in elderly patients with multiple myeloma: updated results of a randomized controlled trial

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The initial analysis of the oral combination melphalan, prednisone, and thalidomide (MPT) in newly diagnosed patients with myeloma showed significantly higher response rate and longer progression-free survival (PFS) than did the standard melphalan and prednisone (MP) combination and suggested a survival advantage. In this updated analysis, efficacy and safety end points were updated. Patients were randomly assigned to receive oral MPT or MP alone. Updated analysis was by intention to treat and included PFS, overall survival (OS), and survival after progression. After a median follow-up of 38.1 months, the median PFS was 21.8 months for MPT and 14.5 months for MP ($P = .004$). The median OS was 45.0 months for MPT and 47.6 months for MP ($P = .79$). In different patient subgroups, MPT improved PFS irrespective of age, serum concentrations of β_2-microglobulin, or high International Staging System. Thalidomide or bortezomib administration as salvage regimens significantly improved survival after progression in the MP group ($P = .002$) but not in the MPT group ($P = .34$). These data confirm activity of MPT for PFS but failed to show any survival advantage. New agents in the management of relapsed disease could explain this finding. The study is registered at www.clinicaltrials.gov as #NCT00232934. (Blood. 2008;112:3107-3114)

Introduction

The combination of melphalan and prednisone (MP) with new agents, such as bortezomib, lenalidomide, or thalidomide, has shown substantial activity in multiple myeloma (MM).[1-9] Four randomized studies have assessed the combination of MP plus thalidomide (MPT) in patients with newly diagnosed MM.[6-9] In our initial report,[6] we compared the oral standard MPT with MP in patients 60 to 85 years of age. The partial response (PR) rates were 76.0% in the MPT group and 47.6% in the MP group. Event-free survival at 2 years was 54% after MPT and 27% after MP ($P = .006$), and overall survival (OS) at 3 years was 80% for MPT and 64% for MP ($P = .19$). In the second study,[7] the Intergroupe Francophone du Myélome (IFM) compared MPT with MP in patients 65 to 75 years of age: PR rates were 76% and 35% ($P < .001$), median progression-free survival (PFS) was 27.5 and 17.8 months ($P < .001$), and median OS was 51.6 and 32.2 months, respectively ($P = .001$). In the third study,[8] the IFM group randomly assigned patients 75 years of age and older to either MPT or MP plus placebo. The PR rate was 62% in the MPT group and 31% in the MP group, median PFS was 24.1 months for MPT and 19.0 months for MP ($P = .001$), and median OS was 45.3 months for MPT and 27.7 months for MP ($P = .03$). In the fourth study,[9] 362 patients with a mean age of 75 years (range, 49-92 years) also received MPT or MP plus placebo. Results of an interim analysis showed better response rate and time to progression in the MPT group than in the MP group ($P < .03$) but did not show any improvement in PFS or OS. Results from these 4 randomized studies[6-9] consistently showed better response rate and remission duration in patients assigned to MPT than in those receiving MP, but OS benefit was only reported in the 2 studies undertaken by the IFM.[7,8] In this updated analysis, we investigated whether MPT can provide improved survival benefit compared with MP after an increased follow-up, and we assessed other updated efficacy endpoints for MPT. We analyzed the relation between the administration of thalidomide or bortezomib as salvage regimens and survival after progression and undertook subgroup analysis for PFS and OS.

Methods

We enrolled 331 patients in 54 centers in Italy. Eligibility criteria were as previously reported.[6] Briefly, we included patients with previously untreated myeloma who were older than 65 years or younger but excluded

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from transplant procedure, had Durie and Salmon stage II or III myeloma,[10] and had measurable disease.[11] The study was approved by the institutional review board at each of the participating centers on January 28, 2002. All patients provided written informed consent before entering the study, which was undertaken in accordance with the Declaration of Helsinki.

Study design and treatment

Study design and randomization procedure were as previously reported.[6] Experimental therapy (MPT) consisted of 6 4-week cycles of oral melphalan (Alkeran; GlaxoSmithKline, Verona, Italy) at 4 mg/m^2 on days 1 through 7, oral prednisone (Deltacortene F; Brunofarmaceutici, Rome, Italy) at a dose of 40 mg/m^2 on days 1 through 7, and oral thalidomide (Pharmion, Windsor, United Kingdom) at 100 mg/day continuously during the 6 cycles of MPT and then at 100 mg/day as maintenance therapy, until evidence of relapse or refractory disease was confirmed. The dose of thalidomide was reduced by 50% on the occurrence of any nonhematologic grade 2 toxicity and was discontinued for any nonhematologic grade 3 toxicity. After 65 patients were randomly assigned to MPT, enoxaparin at 40 mg/day was given subcutaneously during the first 4 cycles of therapy, as anticoagulation prophylaxis. Standard therapy (MP) consisted of six 4-week cycles of oral melphalan at 4 mg/m^2 on days 1 through 7 and oral prednisone at a dose of 40 mg/m^2 on days 1 through 7.

Assessments

Assessments of both efficacy and safety were undertaken every 4 weeks during chemotherapy regimens and every 2 months thereafter. The response to treatment was monitored with the response criteria of European Group for Blood and Marrow Transplantation–International Bone Marrow Transplant Registry.[12] PFS was calculated from the time of diagnosis until the date of progression, relapse, death for any cause, or date that the patient was last known to be in remission. OS was calculated from the time of diagnosis until date of death for any cause or date the patient was last known to be alive. Survival from progression or relapse was calculated from the time of progression or relapse reported after treatment with MPT or MP until the date of death for any cause or date that the patient was last known to be alive. We assessed all adverse events at every visit and graded them according to the National Cancer Institute Common Toxicity Criteria (version 2).[13]

Endpoints and statistical analysis

The primary endpoints were response rates and PFS. Secondary endpoints included OS, prognostic factors, and frequency of any grade 3 or higher adverse events. Sample size was calculated as previously described.[6] Data were monitored by external contract research organization. The final analysis was performed by an independent statistical office. Previously, we reported data from 255 randomized patients[6]; however, in this analysis, we include all 331 randomized patients. Times of observation were censored on December 31, 2007. We calculated the absolute difference (with a 95% confidence interval [CI]) of the proportion of patients in each response category between the 2 groups with CI Analysis (version 2.1.1). Survival data were analyzed with the Kaplan-Meier method,[14] and treatment groups were compared with the log-rank test. The unstratified Cox proportional hazard model was used to estimate the hazard ratios (HRs) and 95% CI for PFS and OS.[15] HR of survival from progression or relapse was adjusted for prognostic factors (age, β_2-microglobulin, albumin) through a multivariate proportional hazards model. Analyses were done with SAS (version 8.2; SAS Institute, Cary, NC).

Results

Patients

Table 1 shows patient demographics and baseline characteristics. A total of 331 patients were randomly assigned to receive oral MPT or MP. At the time of the final analysis, all patients had completed the assigned treatment schedule; 8 (4.8%) of 167 patients in the MPT group and 4 (2.4%) of 164 in the MP group were not treated as assigned. A total of 39 (23.3%) of 167 MPT patients and 37 (22.6%) of 164 MP patients did not complete the assigned treatment schedule (Figure 1). The median duration of thalidomide therapy was 9.6 months (range, 0.03-61.6 months). Thalidomide

Table 1. Baseline clinical characteristics of the 331 patients according to treatment group

	MPT, N = 167	MP, N = 164
Median age, y	72	72
Age, no. (%)		
≤ 65 y	14 (8)	9 (5)
66-70 y	54 (32)	60 (37)
71-75 y	58 (35)	52 (32)
76-80 y	33 (20)	34 (21)
> 80 y	8 (5)	9 (5)
Stage, no. (%)		
IIA	59 (35)	59 (36)
IIB	3 (2)	4 (2)
IIIA	90 (54)	85 (52)
IIIB	15 (9)	16 (10)
M-protein class, no. (%)		
IgG	108 (65)	104 (63)
IgA	41 (24)	43 (26)
Bence Jones protein	18 (11)	17 (11)
Bone marrow plasmacytosis, %		
Median	45	50
Range	5-95	2-95
WHO Performance status, no. (%)*, ≥ 3	10 (6)	8 (5)
Serum β_2-microglobulin		
No. of patients	147	144
Median, mg/L	3.8	3.6
Range, mg/L	0.36-25.4	0.44-37.5
β_2-microglobulin, no. (%)		
≤ 3.5 mg/L	64 (38)	67 (41)
> 3.5 mg/L	83 (50)	77 (47)
Data missing	20 (12)	20 (12)
Albumin		
No. of patients	137	132
Median, g/dL	3.50	3.60
Range, g/dL	2.1-4.9	1.8-4.9
ISS, no. (%)		
No. of patents	136	128
1	32 (23)	32 (25)
2	66 (48)	59 (46)
3	38 (29)	37 (29)
Plasma C-reactive protein		
No. of patients	129	125
Median, mg/L	2.53	2.0
Range, mg/L	0.007-157	0.001-66.7
Hemoglobin		
No. of patients	133	134
Median, g/dL	10.7	10.0
Range, g/dL	7.6-16.2	10.1-15.5
Serum creatinine		
No. of patients	167	164
Median, mg/dL	0.8	0.8
Range, mg/dL	0.6-4.2	0.6-6.8
Serum calcemia		
No. of patients	129	124
Median, mmol/L	2.28	2.27
Range, mmol/L	0.9-3.30	0.9-3.9

MPT indicates melphalan, prednisone, and thalidomide; and MP, melphalan and prednisone.

*Performance status was defined according to the criteria of the World Health Organization (WHO).

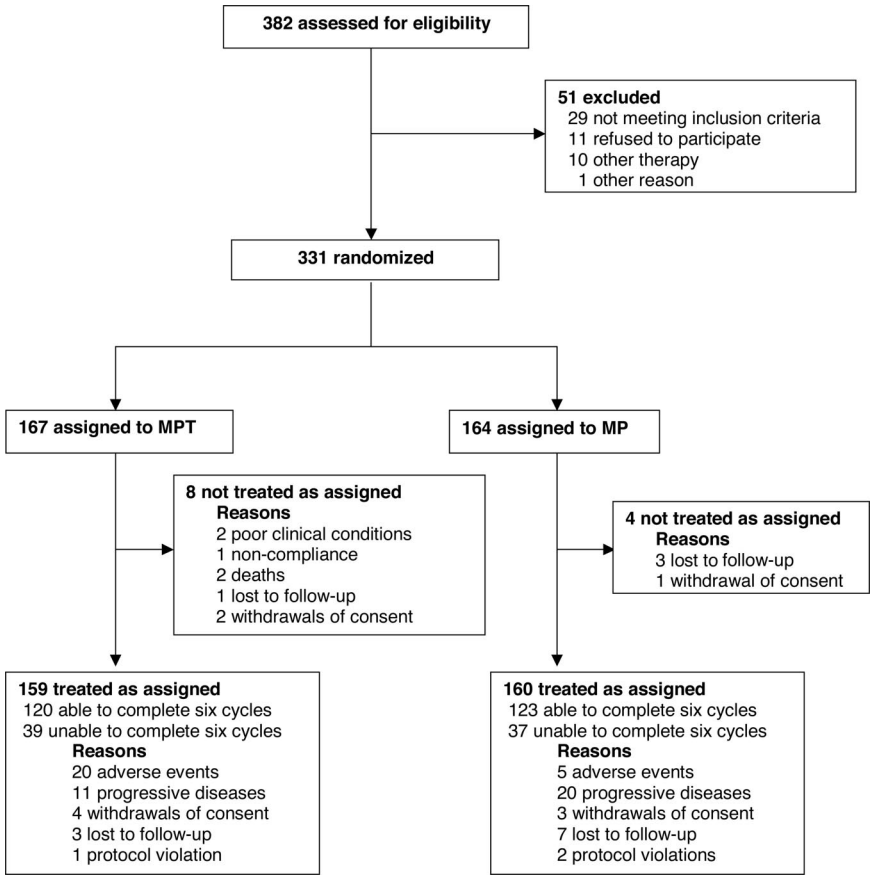


Figure 1. CONSORT diagram. MPT indicates melphalan, prednisone, and thalidomide; and MP, melphalan and prednisone.

was discontinued in 57 (34.1%) patients after a median of 2.2 months, reduced to 50 mg daily in 64 (38.3%) after a median of 6.1 months, and subsequently discontinued in 25 (15.0%) after a median of a further 2.7 months.

Updated end point data

Data were analyzed after a median follow-up of 38.4 months (range, 0.23-69.45 months; SD, 16.5 months) in the MPT group and 37.7 months (range, 0-72.34 months; SD, 17.1 months) in the MP group. A total of 147 (44.4%) patients died in both groups after 21 additional months of follow-up compared with the initial report. The median interval between time of diagnosis and start of treatment was 8 days. In the MPT and MP groups, complete responses were 15.6% and 3.7% (absolute difference = 11.9%; 95% CI, 5.7%-18.5%, $P < .001$), very good partial responses were 29.3 and 11.0 (absolute difference = 18.4%; 95% CI, 9.9%-26.8%, $P < .001$), and partial responses were 68.9 and 47.6 (absolute difference = 21.3%; 95% CI, 10.7%-31.2%, $P < .001$), respectively. The median time to progression was 24.7 and 15.0 months (HR = 0.57; 95% CI, 0.44-0.75; $P < .001$), median PFS was 21.8 and 14.5 months (HR = 0.63; 95% CI, 0.48-0.81; $P < .001$; Figure 2A), but the median OS was 45.0 and 47.6 months, respectively (HR = 1.04; 95% CI, 0.76-1.44, $P = .79$; Figure 2B). A total of 25 deaths (13 from adverse events and 12 from disease progression) were recorded in the MPT group and 25 deaths (10 from adverse events and 15 from disease progression) in the MP group within the first year of treatment.

Subgroup analysis

We confirmed that improved PFS for MPT was consistent across different subgroups that were at increased risk of disease progression, such as patients older than 75 years (HR = 0.53; 95% CI, 0.31-0.91), with increased β_2-microglobulin concentrations (HR = 0.58; 95% CI, 0.40-0.84), with high International Staging System (ISS) disease stage[16] (HR = 0.59; 95% CI, 0.35-1.02), with bone-marrow plasmacytosis (HR = 0.66; 95% CI, 0.45-0.88), with anemia (HR = 0.80; 95% CI, 0.52-1.22), or with renal insufficiency (HR = 0.71; 95% CI, 0.28-1.81; Figure 3). The achievement of at least a very good partial response after 6 months of therapy correlated with better PFS in the entire population (HR = 0.64; 95% CI, 0.45-0.93; $P = .02$), but no significant advantage was evident in the MPT (HR = 0.67; 95% CI, 0.42-1.1; $P = .10$) or in the MP group (HR = 0.74; 95% CI, 0.39-1.39; $P = .35$). OS was unchanged in all prognostic subgroups. In patients with low concentrations of β_2-microglobulin, we noted a trend toward a survival advantage for those assigned to MP (HR = 1.44; 95% CI, 0.80-2.58); conversely, in patients with high concentrations of β_2-microglobulin, we noted a trend toward a survival advantage for those assigned to MPT (HR = 0.70; 95% CI, 0.45-1.08). The difference in survival recorded in these subgroups was marginally significant (P for interact term [MPT*$\beta_2$microglobulin] = .05).

Salvage treatments

The median survival from progression or relapse was shorter in the MPT group than in the MP group (11.5 vs 24.3 months; HR = 1.56; 95% CI, 1.09-2.24, $P = .01$; Figure 4A). A total of 212 (64.0%) patients had progression or relapse: 96 (57.5%) in the MPT group and 116 (70.7%) in

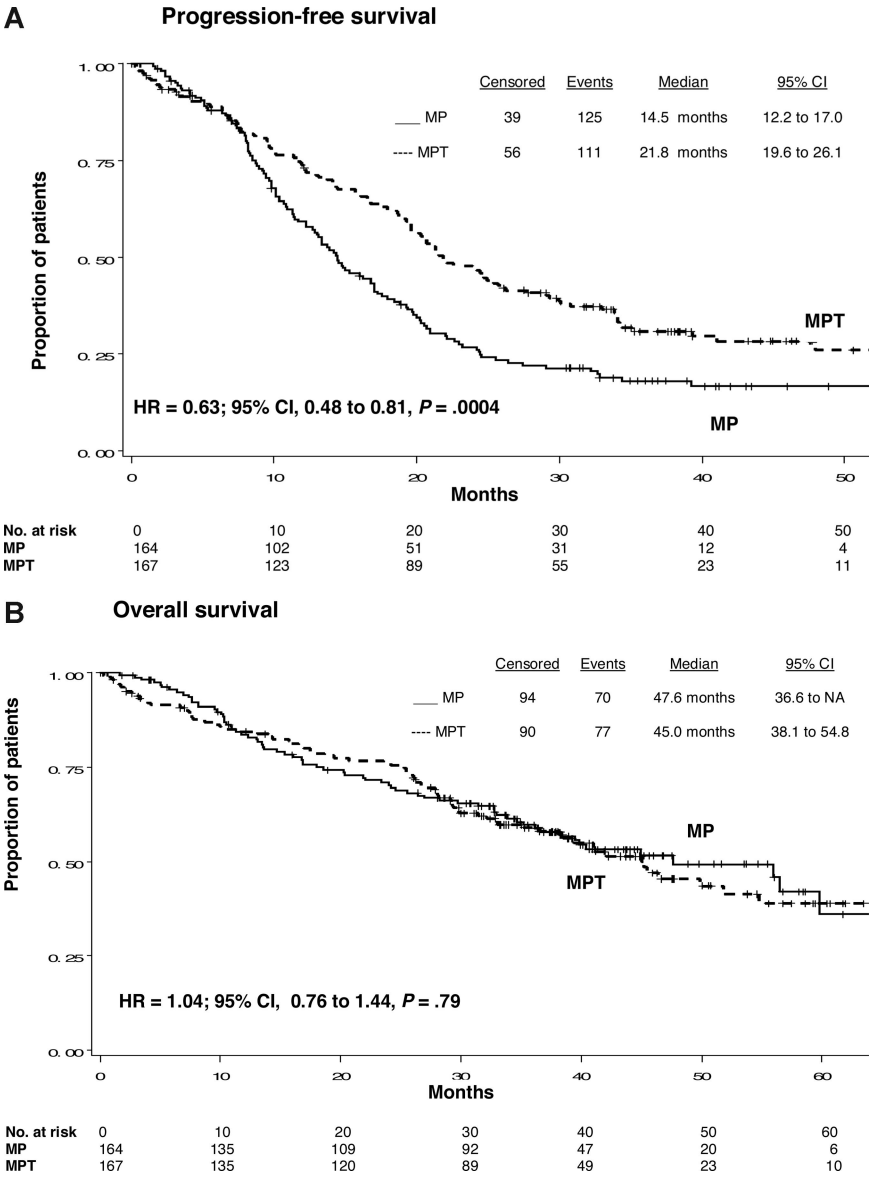


Figure 2. Intention-to-treat population of 331 patients. (A) Progression-free survival. (B) Overall survival. MPT indicates melphalan, prednisone, and thalidomide; MP, melphalan and prednisone; HR, hazard ratio; CI, confidence interval; and NA, not available.

the MP group. A second line of treatment was given in 81 (48.5%) patients assigned to MPT and 93 (56.7%) assigned to MP. 15 (9.0%) MPT patients and 23 (14.0%) MP patients did not receive any salvage regimen, mainly because of death from disease progression. Salvage regimens, including conventional chemotherapies with dexamethasone or doxorubicin, or alkylating agents, were given in 44 (26.3%) MPT patients and 25 (15.2%) MP patients. Bortezomib-based or thalidomide-based salvage regimens were used in 37 (22.2%) MPT patients and 68 (41.5%) MP patients. Bortezomib or thalidomide-based regimens significantly improved survival after progression in patients who received MP at diagnosis (HR = 0.25; 95% CI, 0.12-0.51; $P < .001$; Figure 4B), but not in those who were already exposed to thalidomide at diagnosis in the MPT regimen (HR = 0.75; 95% CI, 0.42-1.35; $P = .34$; Figure 4C). No difference in outcome was observed between patients treated with bortezomib-based or thalidomide-based salvage regimens.

Safety

The MPT safety profile did not differ significantly from the initial report.[6] Grade 3 or 4 adverse events were reported in 92 (55%) MPT patients and in 36 (22%) MP patients. The most frequent grade 3 or 4 adverse events, such as hematologic events (23%), thromboembolism (11%), infections (10%), and gastrointestinal events (5%), were virtually identical. After the introduction of enoxaparin prophylaxis, grade 3 or 4 thromboembolism was reported in 3 patients. Two of these patients had evidence of thromboembolism within 2 months after the discontinuation of enoxaparin. No late thromboembolic events were reported. Neurologic events were 14% (previous report, 10%), cardiac events were 10% (previous report, 7%), and dermatologic events were 6% (previous report, 3%). Grade 3 or 4 neurologic toxicity was reported in 24 (14%) patients. Peripheral neuropathy was the most frequent neurologic adverse event, observed in 16 (10%) patients.

Discussion

In this updated analysis, oral MPT showed better response rate and duration of remission duration than did standard MP. We recorded no increased frequency of serious adverse events after an extended follow-up. These results accord with those from our initial analysis.[6] Our previous analysis[6] suggested better OS for

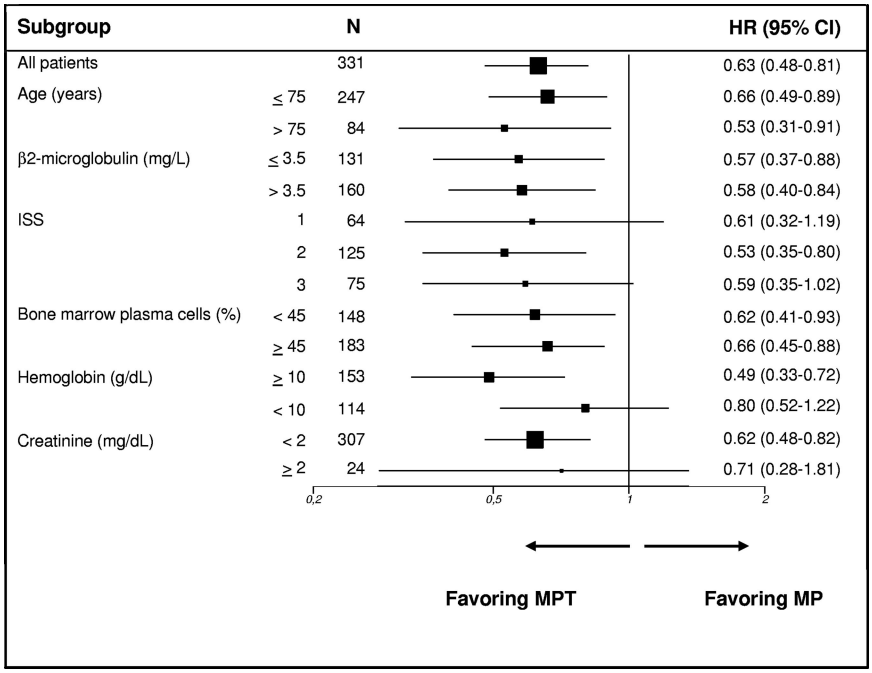
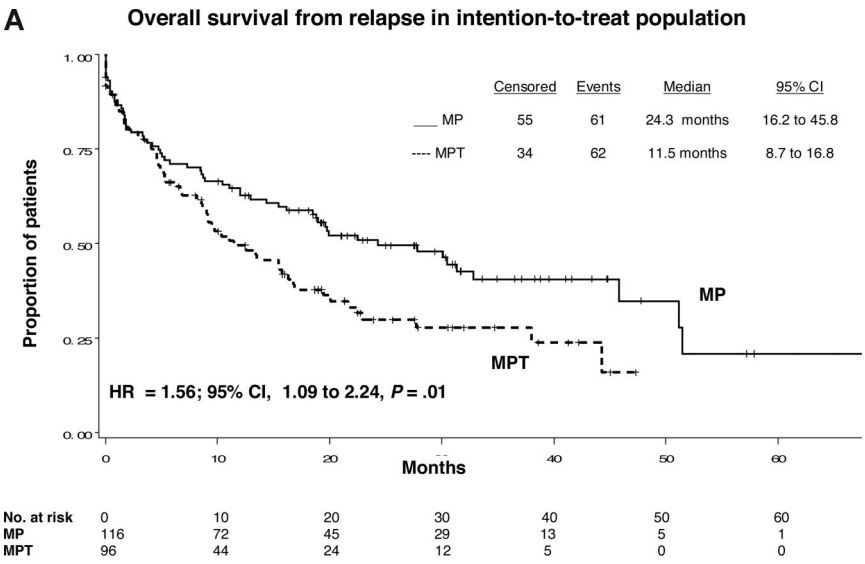
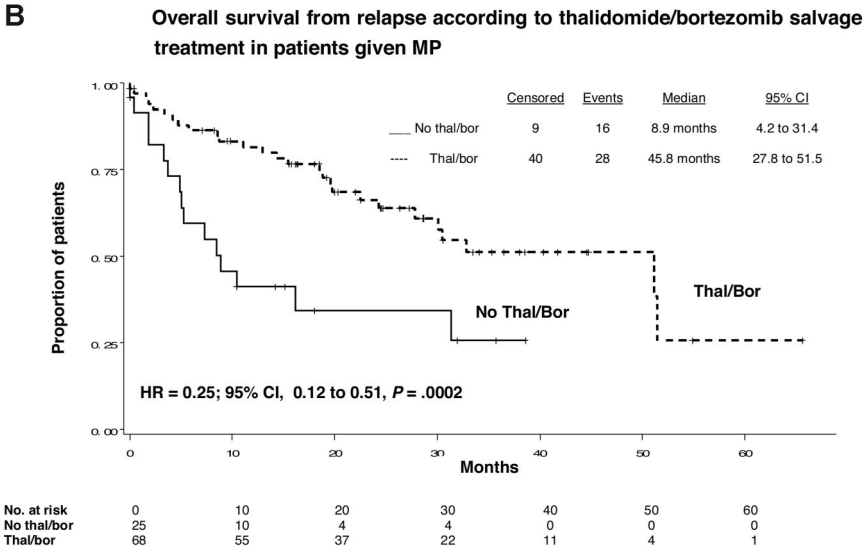


Figure 3. Subgroup analysis. Hazard ratio (HR) estimates for progression-free survival. MPT indicates melphalan, prednisone, and thalidomide; MP, melphalan and prednisone; CI, confidence interval; and ISS, International Staging System.

the MPT group (HR = 0.68; 95% CI, 0.38-1.22), but results from the extended follow-up failed to confirm this difference. With an increased follow-up, the survival curves are now almost identical in both MPT and MP groups. A substantial number of patients crossover from the MP group to thalidomide-based or bortezomib-based salvage regimens after relapse or progression.[17-21] The crossover could explain the absence of survival advantage. At the time of the first relapse, combinations including thalidomide or bortezomib were given to 22.2% of MPT patients and 41.5% of MP patients, whereas chemotherapy only was administered in 26.3% of MPT patients and 15.2% of MP patients. Survival from progression or relapse was significantly improved in patients who received MP at diagnosis and new agents as a second line of therapy, but not in those who received MPT as the induction regimen. Relapses in the MPT group seemed to be more drug-resistant than were those in the MP group. A higher rate of failure with salvage therapy and shorter survival after relapse can partly explain the similar OS rates in the 2 groups. In the study undertaken by the IFM,[7] a statistically significant OS advantage was reported in patients who received MPT. Salvage therapies including thalidomide or bortezomib were given to 31% of MPT patients and 46% of MP patients. Despite this substantial crossover, survival from relapse was almost identical in both groups. Comparisons between different studies are difficult to make because of differences in patient populations, duration of treatment, and use of maintenance regimen. Major differences between our study and the IFM study[7] are: age of patients (patients aged ≥ 70 years, 69% vs 40%), number of MP cycles (6 vs 12 cycles), dose of thalidomide (100 mg vs up to 400 mg), and presence or absence of a thalidomide-maintenance regimen. The reason for the absence of OS advantage in our study and its presence in the IFM study is difficult to establish.[7] The occurrence of drug-resistant relapse should be much the same in both studies, although future studies should better define if a thalidomide maintenance approach may increase the incidence of drug-resistant relapse. The total dose of melphalan was 4 mg/kg in patients who completed the assigned treatment schedule of our study (6 MPT cycles) but 12 mg/kg in those who received the assigned 12 cycles of the IFM study. An increased dose of melphalan can induce a higher frequency of cumulative hematologic toxic effects and long-lasting thrombocytopenia.[22] The occurrence of peripheral cytopenia prevents the delivery of full-dose second-line therapies, reducing the effect of salvage therapies on survival. The median OS for MPT patients was fairly similar in both studies[6,7] (45 months vs 51.6 months), but the median OS for MP patients was substantially higher in our study (47.6 months vs 33.2 months), even though median age was much higher. These data suggest that thalidomide exerted its benefit at diagnosis in both studies but failed to improve outcome in patients who received a higher dose of melphalan at diagnosis and who were salvaged with a regimen containing thalidomide or bortezomib at relapse. Two other independent studies comparing MPT with MP have reported similar controversies, but they are not yet available as full publications.[8,9] Patients assigned to MPT had improved time to progression in both studies, but survival advantage was reported only in one study[8] and not in the other.[9] Whether a sequential treatment with a single agent would yield similar survival benefits with fewer toxic effects compared with a more complex combinational regimen given at diagnosis remains unknown. If a combinational approach is better than single-agent therapy, this option should be considered at diagnosis when there is the best chance to induce a greater duration of remission. A sequential approach should then be considered at first and subsequent relapses, when less intense and more palliative regimens are needed. Subgroup analysis, not shown in our previous report,[6] confirmed that improved PFS for MPT was consistent across different subgroups that had an increased risk of disease progression (ie, patients older than 75 years and those with raised β_2-microglobulin concentrations, high ISS disease stage, bone-marrow plasmacytosis, anemia, or renal insufficiency). OS was unchanged in all subgroups. In patients with low concentrations of β_2-microglobulin, we noted a trend toward a survival advantage for patients assigned to MP. We recorded slight differences in the rate of serious adverse events between this





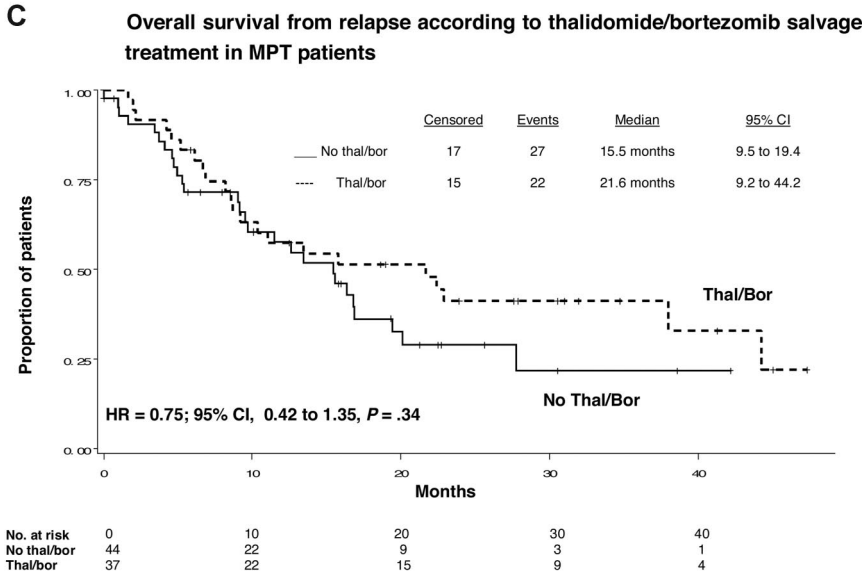


Figure 4. Survival after progression or relapse in intention-to-treat population and according to thalidomide or bortezomib salvage-treatment. Overall survival from relapse in intention-to-treat population (A), according to thalidomide/bortezomib salvage treatment for melphalan and prednisone patients (B) and for melphalan, prednisone, thalidomide (C). MPT indicates melphalan, prednisone, and thalidomide; MP, melphalan and prednisone; HR, hazard ratio; CI, confidence interval; Thal, thalidomide; and Bor, bortezomib.

updated and the initial analyses.[6] We identified no new safety concerns in this updated analysis and no evidence of new or cumulative toxic effects. Peripheral neuropathy remains the major adverse event, which is quite manageable with appropriate thalidomide dose reduction. No late thromboembolic events were noted after the discontinuation of anticoagulant prophylaxis. In the previous report,[6] overall survival was not significant with a trend in favor of MPT (HR = 0.68), whereas survival from relapse and subgroup analyses was not reported. In this updated analysis, the lack of an overall survival benefit is rather definitive, and longer follow-up will not change the results; survival from relapse is improved by the introduction of new drugs in salvage regimens; subgroup analyses show that the MPT benefit is identical in patients with high or low levels of β_2-microglobulin, and no additional or late adverse events are present.

In conclusion, MPT continues to show a better response and PFS in elderly patients with newly diagnosed MM than standard MP does. However, we noted no advantage in OS, probably because of the use of more effective salvage regimens in the control group.

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Authorship

Contribution: A.P., S.B., F.C., F.G., P.F., and M.B. collected and revised material and wrote the paper; and A.M.L., T.C., A.F., V.C., M.M., R.R., A.C., R.Z., G.B., D.D., F.D., G.C., P.M., and M.C. revised material and wrote the paper.

Conflict-of-interest disclosure: A.P. and M.B. have served on scientific advisory boards and speakers' bureaus for Pharmion and Celgene. P.M. has received honoraria from Pharmion. The remaining authors declare no competing financial interests.

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Appendix

In addition to the authors, the following investigators (listed in alphabetical order) participated in this study: ALBA: Oncologia Medica, ASL18, Dr Galliano; ALESSANDRIA: Divisione di Ematologia, Az. Osp. "SS. Antonio e Biagio e C. Arrigo," Prof Levis, Dr ssa Baraldi; BERGAMO: Divisione di Ematologia, Ospedali Riuniti, Prof Barbui, Dr ssa Galli; BRA, Divisione di Medicina, Ospedale S. Spirito, Dott. Vanni, Dr ssa Stefani; CATANIA: Cattedra di Ematologia, Ospedale Ferrarotto, Prof Giustolisi, Prof Di Raimondo; CATANZARO: Unità Operativa Ematologia, Az. Osp. Pugliese-Ciacco, Dr Piro; CREMONA: Unità di Ematologia, Az. Istituti Ospitalieri, Dr Morandi; CUNEO: Divisione di Ematologia, Ospedale Civico S. Croce e Carle, Prof Gallamini, Dr ssa Grasso; FORLI: Dipartimento di Onco-ematologia, Ospedale Morgagni, Dr Amadori, Dr ssa Ronconi; MESSINA: Unità Operativa di Ematologia, Azienda Ospedaliera Papardo, Dr ssa Brugiatelli, Dr Quartarone; MONZA: Semeiotica Medica e U.D.A. Trapianto Midollo Osseo, Università degli Studi di Milano, Prof Pogliani, Dr Rossini; NAPOLI: Divisione di Ematologia, Università Federico II, Policlinico, Prof Rotoli, Dr Catalano; ORBASSANO: Divisione di medicina Interna II, Ospedale San Luigi, Prof Saglio, Dr ssa Guglielmelli; PALERMO: Unità Operativa di Ematologia I, Az. Osp. Cervello, Prof Mirto, Dr ssa Cangialosi; PERUGIA: Sezione di Medicina Interna e Scienze Oncologiche, Azienda Ospedaliera di Perugia, Prof ssa Liberati; PINEROLO: Divisione di Medicina, Asl 10, Dr Griso; RAVENNA: Sezione di Ematologia, Ospedale Santa Maria delle Croci, Dr Zaccaria; RIETI: Ospedale San Camillo de Lellis, Dott. Capparella; ROMA: Divisione di Ematologia, Policlinico Umberto I, Università La Sapienza, Prof Foà, Dr ssa Petrucci, Divisione di Ematologia, Policlinico Gemelli, Università La Cattolica, Prof Leone, Prof De Stefano, S.C. Ematologia, Ospedale Regina Elena, Prof ssa Petti, Dr Pisani, Divisione di Ematologia, Ospedale San Giovanni Addolorata, Prof ssa Annino, Dr ssa Bongarzoni; ROZZANO: Dipartimento di Oncoematologia Medica, Istituto Clinico Humanitas, Dr Nozza, Dr Castagna; TORINO: Unità Operativa di Ematologia, Ospedale Evangelico Valdese, Dr Bazzan, Dr ssa Rus, U.O Ematologia, Ospedale Mauriziano Umberto I, Prof Poccardi, Dr ssa Gottardi, Divisione di Medicina, Az. Osp. San Giovanni Battista, Ospedale S. Vito, Dr Marinone, Dr ssa Picara; VICENZA: Divisione di Ematologia, Ospedale San Bortolo, Prof Rodeghiero, Dr ssa Elice.

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