

# Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial

Antonio Palumbo, Sara Bringhen, Tommaso Caravita, Emanuela Merla, Vincenzo Capparella, Vincenzo Callea, Clotilde Cangialosi, Mariella Grasso, Fausto Rossini, Monica Galli, Lucio Catalano, Elena Zamagni, Maria Teresa Petrucci, Valerio De Stefano, Manuela Ceccarelli, Maria Teresa Ambrosini, Ilaria Avonto, Patrizia Falco, Giovannino Ciccone, Anna Marina Liberati, Pellegrino Musto, Mario Boccadoro, for the Italian Multiple Myeloma Network, GIMEMA\*

## Summary

**Background** Since 1960, oral melphalan and prednisone (MP) has been regarded as the standard of care in elderly multiple myeloma patients. This multicentre randomised trial compared oral MP plus thalidomide (MPT) with MP alone in patients aged 60–85 years.

**Methods** Patients with newly diagnosed multiple myeloma were randomly assigned to receive oral MP for six 4-week cycles plus thalidomide (n=129; 100 mg per day continuously until any sign of relapse or progressive disease) or MP alone (n=126). Analysis was intention-to-treat. This study is registered at ClinicalTrials.gov, number NCT00232934.

**Results** Patients treated with thalidomide had higher response rates and longer event-free survival (primary endpoints) than patients who were not. Combined complete or partial response rates were 76·0% for MPT and 47·6% for MP alone (absolute difference 28·3%, 95% CI 16·5–39·1), and the near-complete or complete response rates were 27·9% and 7·2%, respectively. 2-year event-free survival rates were 54% for MPT and 27% for MP (hazard ratio [HR] for MPT 0·51, 95% CI 0·35–0·75, p=0·0006). 3-year survival rates were 80% for MPT and 64% for MP (HR for MPT 0·68, 95% CI 0·38–1·22, p=0·19). Rates of grade 3 or 4 adverse events were 48% in MPT patients and 25% in MP patients (p=0·0002). Introduction of enoxaparin prophylaxis reduced rate of thromboembolism from 20% to 3% (p=0·005).

**Conclusion** Oral MPT is an effective first-line treatment for elderly patients with multiple myeloma. Anticoagulant prophylaxis reduces frequency of thrombosis. Longer follow-up is needed to assess effect on overall survival.

## Introduction

The incidence of multiple myeloma in men is about 5·0 and in women about 4·2 per 100 000 person-years. Diagnosed patients who are older than 65 years account for 66% of all new cases and for 75% of all deaths from myeloma.<sup>1</sup> High-dose chemotherapy with haemopoietic stem-cell support increases the rate of complete response and extends event-free and overall survival.<sup>2–4</sup> However, this approach is generally suitable for patients younger than 65 years, who represent only about a third of all myeloma patients.<sup>1</sup> A meta-analysis of 6633 patients from 27 randomised trials showed that melphalan and prednisone (MP) was not better than combination chemotherapy.<sup>5</sup> For patients older than 65 years, conventional chemotherapy has remained the treatment of choice since 1960. So far no major improvement in outcome from the original MP combination has been achieved<sup>5–8</sup> in these patients, and new treatments are urgently needed.

Several properties of thalidomide form the empirical basis for its clinical use. Proposed mechanisms include: inhibition of tumour necrosis factor  $\alpha$ , suppression of angiogenesis, increase in cell-mediated cytotoxic effect, and alteration of expression of cellular adhesion molecules.<sup>9–11</sup> Treatment approaches using thalidomide

in combination with dexamethasone or chemotherapy agents attempt to take advantage of their additive or synergistic activity, and often induce relatively high rates of profound tumour regression, compared with those achieved with conventional therapy.<sup>6,12–20</sup> The response rate of relapsed myeloma to thalidomide ranges from 25% to 35%.<sup>12–14</sup> When thalidomide is used in combination with corticosteroid, the response rate increases to about 50%,<sup>15,16</sup> and around 70% when used in combination with alkylating agents.<sup>17–20</sup>

Sedation, fatigue, and constipation are common but manageable adverse events of thalidomide.<sup>21</sup> The incidence of deep-vein thrombosis increases in patients with newly diagnosed myeloma compared with those with relapsed and refractory disease, especially if thalidomide is given with chemotherapeutic drugs.<sup>22–24</sup> Anticoagulant treatment might reduce the incidence of this adverse event.<sup>24,25</sup> Peripheral neuropathy occurs with long-term use of thalidomide and often necessitates discontinuation of the drug, although dose reduction might improve symptoms.<sup>26,27</sup> Use of thalidomide in pregnancy is absolutely contraindicated and prescription safety programmes<sup>28</sup> must be followed to prevent teratogenic effects.

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\*Participants listed at end of report

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Divisione di Ematologia dell'Università di Torino, Azienda Ospedaliera S Giovanni Battista, 10126 Torino, Italy (A Palumbo MD, S Bringhen MD, M T Ambrosini MD, I Avonto MD, P Falco MD, Prof M Boccadoro MD); Cattedra e Divisione di Ematologia, Università Tor Vergata, Ospedale S Eugenio, Roma, Italy (T Caravita MD); UO di Ematologia e Trapianto di Cellule Staminali, IRCCS Casa Sollievo della Sofferenza, S Giovanni Rotondo, Italy (E Merla MD); UO di Ematologia, Centro di Riferimento Oncologico Regionale, Rionero in Vulture, Italy (P Musto MD); Ospedale San Camillo de Lellis, Rieti, Italy (V Capparella MD); Divisione di Ematologia, Ospedali Riuniti, Reggio Calabria, Italy (V Callea MD); Divisione di Ematologia e Trapianto di Midollo Osseo, Azienda Ospedaliera Cervello, Palermo, Italy (C Cangialosi MD); Divisione di Ematologia, Azienda Ospedaliera S Croce e Carle, Cuneo, Italy (M Grasso MD); Ematologia, H S Gerardo, Monza, Italy (F Rossini MD); Divisione di Ematologia, Ospedali Riuniti, Bergamo, Italy (M Galli MD); Cattedra e Divisione di Ematologia, Università Federico II, Napoli, Italy (L Catalano MD); Istituto di Ematologia e Oncologia Medica "Seragnoli", Università di Bologna, Italy (E Zamagni MD); Dipartimento di biotecnologie ed Ematologia, Università La Sapienza, Roma, Italy (M T Petrucci MD); Istituto di Ematologia, Università Cattolica, Roma, Italy (Prof V De Stefano MD); Unità di Epidemiologia dei Tumori, Azienda Ospedaliera S Giovanni Battista, and CPD Piemonte, Torino, Italy (M Ceccarelli MD, G Ciccone MD); and Clinica Medica I, Policlinico Monteluce, Perugia, Italy (Prof A M Liberati MD)

Correspondence to: Dr Antonio Palumbo [appalumbo@yahoo.com](mailto:appalumbo@yahoo.com)

Thalidomide alone or in combination has been increasingly adopted as first-line treatment for newly diagnosed myeloma, despite the paucity of data from randomised trials. These observations provide the rationale for our prospective, open-label, unblinded, multicentre randomised trial of oral MP with or without thalidomide for the treatment of patients with newly diagnosed myeloma.

## Methods

### Patients

The trial was done at 54 centres in Italy from January, 2002, to May, 2005. Inclusion criteria were previously untreated myeloma patients who were older than 65 years (or younger but unable to undergo transplantation), Durie and Salmon stage II or III myeloma, and measurable disease. Patients agreed to use contraception, and women of childbearing age had a pregnancy test before enrolment. Exclusion criteria were another cancer, psychiatric disease, and any grade 2 peripheral neuropathy. Abnormal cardiac function, chronic respiratory disease, and abnormal liver or renal functions were not criteria for exclusion. The study was approved by the institutional review board at each participating centre. All patients gave written informed consent before entering the study, which was done in accordance with the Declaration of Helsinki.

### Study design and procedures

A simple randomisation sequence was generated by a centralised computer. After registration in a centralised

database through the internet and validation of eligibility, patients were randomly allocated to treatments by use of an automated assignment procedure concealed from the investigators. Experimental therapy (MPT) consisted of oral administration of melphalan at 4 mg/m<sup>2</sup> on days 1–7 and oral prednisone at a dose of 40 mg/m<sup>2</sup> on days 1–7. Each cycle was repeated every 4 weeks. A standard number of six cycles was given. Thalidomide (Pharmion, Windsor, UK) was administered at 100 mg per day continuously during the six MPT cycles, and then at 100 mg per day, as maintenance therapy, until confirmed evidence of relapse or refractory disease. The dose of thalidomide was reduced by 50% on the occurrence of any non-haematological grade 2 toxic effects and the drug was discontinued for any non-haematological grade 3 toxic effects. No anticoagulation prophylaxis was given until December, 2003, when the protocol was amended, and enoxaparin at 40 mg per day was delivered subcutaneously during the first four cycles of therapy. Standard therapy consisted of oral melphalan given at 4 mg/m<sup>2</sup> on days 1–7 and oral prednisone at 40 mg/m<sup>2</sup> on days 1–7, every 4 weeks for six cycles. In the MP group, no planned maintenance therapy was given. In this group, patients who had progressive disease or relapse were permitted to crossover to receive thalidomide as salvage treatment.

The primary objective was to compare clinical response rates and event-free survival in the two treatment groups. Secondary endpoints included overall survival, prognostic factors, time to the first evidence of response, and incidence of any grade 3 or higher adverse events. Data were collected and monitored by the investigators, and the final analysis was done by an independent statistical office.

The response to treatment was monitored by measurement of protein in serum and urine at each participating centre every 4 weeks. The response rate was assessed at 6 months. We used the response criteria of the European Group for Blood and Marrow Transplantation/International Bone Marrow Transplant Registry.<sup>29</sup> Briefly, complete response required disappearance of myeloma protein in serum and urine and negative immunofixation. Partial response required at least 50% reduction of myeloma protein in serum and a 90% decrease in urine. Near-complete response, a subcategory of partial response, required disappearance of myeloma protein in serum and urine, with positive immunofixation. Minimal response was defined as a reduction of myeloma protein in serum of 25–49% and in urine of 50–89%. A reduction in myeloma protein of 24% or less was classified as no response. Progressive disease was defined as an increase of 25% or greater in myeloma protein.

Responses were confirmed after a further 6 weeks. Bone-marrow plasmacytosis and skeletal disease were included in response evaluation.

Event-free survival was calculated from the time of diagnosis until the date of progression, relapse, death for any cause, or the date the patient was last known to be in

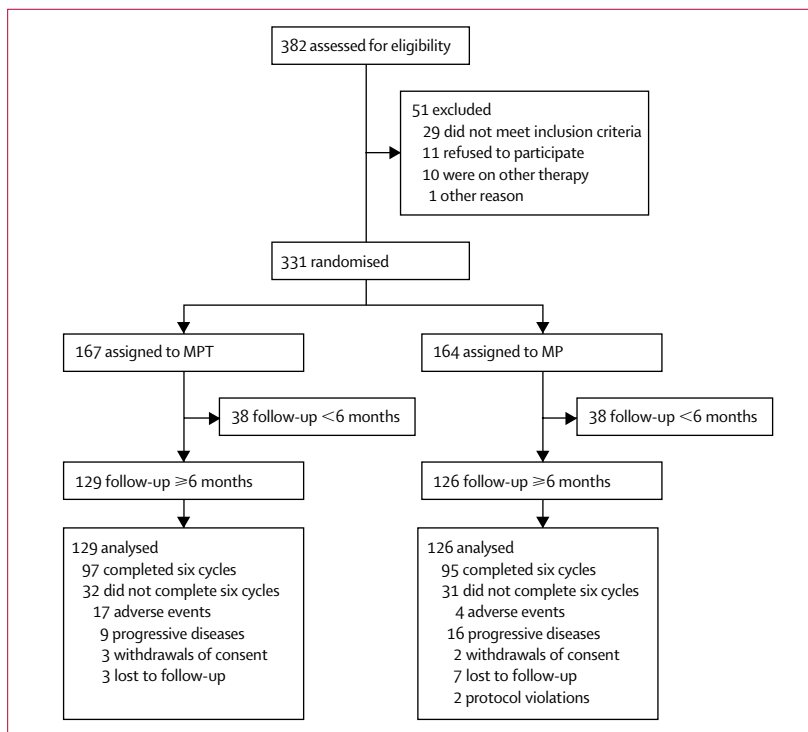


Figure 1: Trial profile

remission. Overall survival was calculated from the time of diagnosis until the date of death for any cause or the date the patient was last known to be alive.

All adverse events were assessed at each visit and graded according to the National Cancer Institute Common Toxicity Criteria (version 2). Causes of death were recorded as attributable to myeloma, study drugs, other causes, or a combination of these. Thromboembolism was assessed by clinically objective evidence of thrombosis and by use of ultrasound echography. A complete neurological evaluation was done during initial screening, during treatment as needed, and at the end of treatment. Assessments of both efficacy and safety were done every 4 weeks during chemotherapy regimens and every 2 months thereafter.

### Statistical analysis

A sample size of 380 patients (190 per arm) was required to detect a 10% increase in complete response in the MPT arm (from 5% to 15%), with an  $\alpha$  error of 0.05 and a  $\beta$  error of 0.10. Two interim analyses were done during the trial. The first interim analysis was done for safety monitoring. At the second interim analysis, the MPT group showed a significant improvement in the response rate ( $p < 0.0001$ ) and prolongation of event-free survival ( $p = 0.0006$ ) compared with the MP group. These results, and the falling enrolment, convinced the steering committee to stop the trial in May, 2005, after 331 patients had been randomised (87% of the planned sample size). For the present analysis, all 255 patients with at least 6 months of follow-up (minimum time required to evaluate clinical response, primary endpoint) were included. Times of observation were censored on June 15, 2005. Analyses were done on an intention-to-treat basis.

The absolute difference (with 95% CI) of the proportion of patients in each response category between the two groups was calculated with CI Analysis, version 2.1.1. Survival data were analysed with the Kaplan-Meier method,<sup>30</sup> and treatment groups compared with the log-rank test. The Cox proportional hazard model was used to estimate HR and 95% CI. Further subgroup analyses were done with the Cox model to detect clinically relevant interactions between treatment and prognostic factors (ie, age and  $\beta_2$  microglobulin in serum). The incidence of any adverse event was compared by the  $\chi^2$  test or Fisher's exact test when cell counts were lower than five. The analyses were performed with SAS (version 8.2).

This study is registered at ClinicalTrials.gov, number NCT00232934.

### Role of the funding source

Pharmion supplied free thalidomide for this study; the company had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit this manuscript for publication.

|   | MPT (n=129)      | MP (n=126)       |
|---|------------------|------------------|
| <b>Age</b>                                |                  |                  |
| Median (years)                            | 72               | 72               |
| <65 years                                 | 4 (3%)           | 3 (2%)           |
| 65–70 years                               | 49 (38%)         | 51 (41%)         |
| 71–75 years                               | 44 (34%)         | 37 (29%)         |
| 76–80 years                               | 26 (20%)         | 28 (22%)         |
| >80 years                                 | 6 (5%)           | 7 (6%)           |
| <b>Stage</b>                              |                  |                  |
| IIA                                       | 50 (39%)         | 49 (39%)         |
| IIB                                       | 4 (3%)           | 3 (2%)           |
| IIIA                                      | 64 (50%)         | 62 (49%)         |
| IIIB                                      | 11 (8%)          | 12 (10%)         |
| <b>Myeloma protein class</b>              |                  |                  |
| IgG                                       | 83 (64%)         | 73 (58%)         |
| IgA                                       | 31 (24%)         | 37 (29%)         |
| Bence Jones protein                       | 15 (12%)         | 16 (13%)         |
| <b>Bone-marrow plasmacytosis</b>          |                  |                  |
| Median (range)                            | 45 (5–95)        | 46 (5–95)        |
| <b>WHO performance status</b>             |                  |                  |
| $\geq 3$                                  | 9 (7%)           | 6 (4%)           |
| <b><math>\beta_2</math> microglobulin</b> |                  |                  |
| n   | 116              | 110              |
| Median (range [mg/L])                     | 3.7 (0.36–40)    | 3.7 (0.2–37.5)   |
| $\leq 3.5$ mg/L                           | 53 (41%)         | 53 (42%)         |
| $> 3.5$ mg/L                              | 63 (49%)         | 57 (45%)         |
| Data missing                              | 13 (10%)         | 16 (13%)         |
| <b>C-reactive protein</b>                 |                  |                  |
| n   | 105              | 100              |
| Median (range [mg/L])                     | 2.53 (0.005–157) | 2.0 (0.001–128)  |
| <b>Haemoglobin</b>                        |                  |                  |
| n   | 125              | 122              |
| Median (range [g/L])                      | 106 (73–147)     | 102 (67–155)     |
| <b>Creatinine</b>                         |                  |                  |
| n   | 129              | 125              |
| Median (range [mg/L])                     | 8 (5.6–102)      | 8 (6–68)         |
| <b>Calcium</b>                            |                  |                  |
| n   | 115              | 118              |
| Median (range [mmol/L])                   | 2.25 (1.22–3.17) | 2.27 (1.09–2.72) |

Data are number (%) unless otherwise stated.

**Table 1: Baseline clinical characteristics**

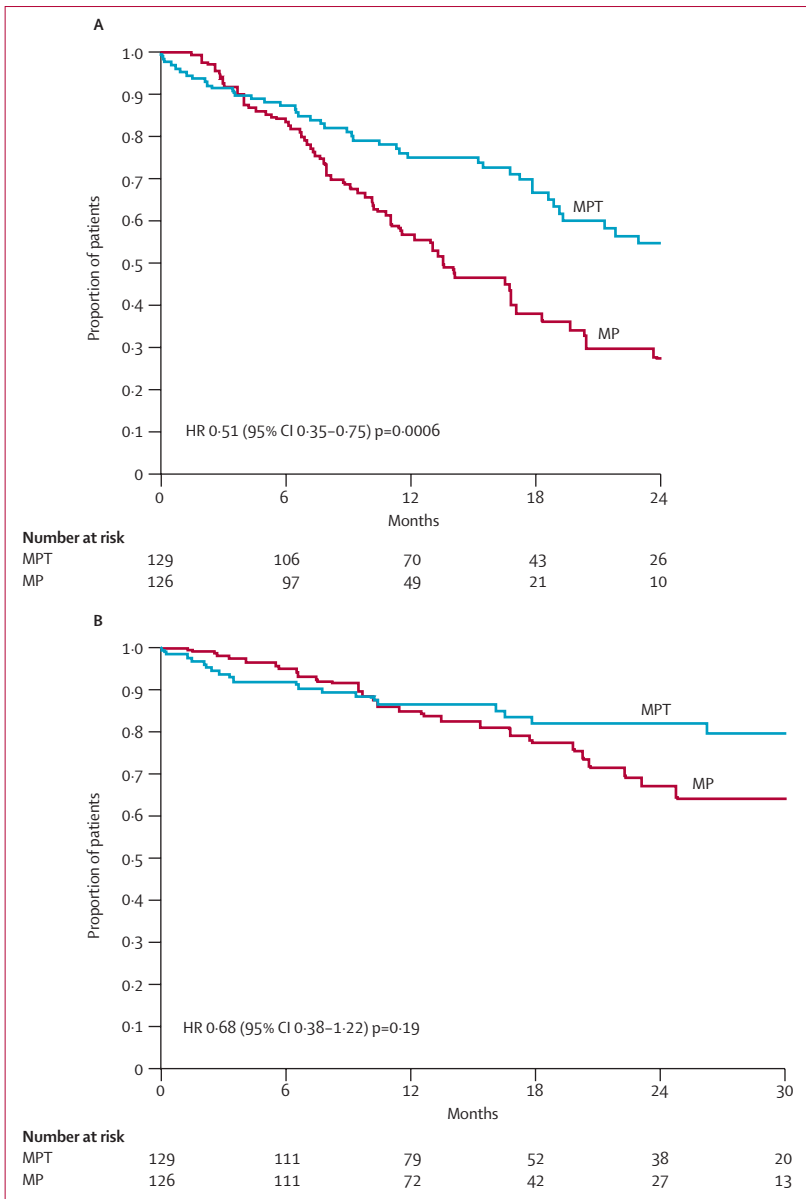
### Results

255 patients were randomly assigned to receive oral MPT or MP. At the time of the analysis, all patients had completed the assigned treatment schedule (figure 1). 25% of patients in both groups did not complete the assigned six cycles. Before introduction of anticoagulant

|                                      | Number (%) patients |            | Absolute difference |                 |
|--------------------------------------|---------------------|------------|---------------------|-----------------|
|                                      | MPT (n=129)         | MP (n=126) | MPT–MP (95% CI)     |                 |
| Complete or partial response         | 98 (76.0%)          | 60 (47.6%) | 28.3%               | (16.5 to 39.1)  |
| Complete response†                   | 20 (15.5%)          | 3 (2.4%)   | 13.1%               | (6.3 to 20.5)   |
| Partial response                     | 78 (60.4%)          | 57 (45.2%) | 15.2%               | (3.0 to 26.9)   |
| Near-complete response               | 16 (12.4%)          | 6 (4.8%)   | ..                  |                 |
| 90% to 99% myeloma protein reduction | 11 (8.5%)           | 6 (4.8%)   | ..                  |                 |
| 50% to 89% myeloma protein reduction | 51 (39.5%)          | 45 (35.7%) | ..                  |                 |
| Minimal response                     | 7 (5.4%)            | 21 (16.7%) | –11.2%              | (–19.2 to –3.6) |
| No response                          | 7 (5.4%)            | 19 (15.1%) | –9.7%               | (–17.4 to –2.2) |
| Progressive disease                  | 10 (7.8%)           | 21 (16.7%) | –8.9%               | (–17.2 to –0.8) |
| Not available*                       | 7 (5.4%)            | 5 (4.0%)   |                     |                 |

†Disappearance of myeloma protein; immunofixation-negative. \*12 patients were not assessed because follow-up was less than 1 month owing to early death (two), lost to follow-up (nine), and withdrawal of consent (one).

**Table 2: Clinical response**



**Figure 2: (A) Event-free survival and (B) overall survival**  
 The survival curves cross at about 9 months because of the higher proportion of deaths in the MPT group (11 for adverse events, two for disease progression) than in the MP group (four for adverse events and six for disease progression). Thereafter a lower proportion of deaths in the MPT group (seven for disease progression) was observed than in the MP group (15 for disease progression, two for adverse events).

prophylaxis, 11 of 65 MPT patients (17%) did not complete the assigned six cycles for adverse events; after introduction of enoxaparin, six of 64 patients (9%) did not finish the planned treatment. The median duration of thalidomide therapy was 8 months (range 0.03–39.4). Thalidomide was discontinued in 43 patients after a median of 2.1 months, reduced to 50 mg in 37 patients after a median of 4 months, and subsequently in ten of 37 patients after a median of 5.3 months. Baseline demographics and other characteristics of the two groups were balanced (table 1).

A greater proportion of patients in the MPT group than in the MP group had a complete or partial response, assessed at 6 months (table 2). Median time to partial response was 1.4 months (range 22–200 days) in the MPT group and 3.1 months (25–210 days) in the MP group. In the MPT group, 11 patients showed a further improvement in response rate during maintenance with thalidomide. Near-complete or complete responses were achieved in 36 of the 129 patients (27.9%) who received thalidomide, compared with nine of the 126 patients (7.2%) who did not.

The median duration of follow-up from diagnosis was 17.6 months (range 0.23–44.3; SD 11.2) for survivors in the MPT group and 15.2 months (0.06–43.2; 11.2) for survivors in the MP group.

Progression, relapse, or death occurred in 42 of 129 patients in the MPT group (33%), and 62 of 126 (49%) in the MP group. The 2-year event-free survival rate was 54% in patients receiving MPT and 27% in patients receiving MP—a 49% decrease in risk of events in the MPT group (HR 0.51, 95% CI 0.35–0.75,  $p=0.0006$ ; figure 2). Subgroup analyses did not show any statistical or clinical difference between the groups in treatments, age, or  $\beta_2$  microglobulin concentration in serum. In patients older than 70 years, the HR of the event-free survival was 0.45 (95% CI 0.26–0.77). In those younger than 70 years, the HR was 0.61 (0.35–1.06).

20 patients (16%) died in the MPT group and 27 (21%) in the MP group. The overall 3-year survival rate was 80% in patients taking thalidomide and 64% in those not taking thalidomide (figure 2). In the MPT group, 13 deaths (11 from adverse events and two from disease progression, median age 75 years) were reported within the first 9 months of treatment, compared with ten in the MP group (four adverse events and six disease progression, median age 77 years). In the MPT group, a higher proportion of deaths from toxic effects negatively affected earlier phases of overall survival. During the first 9 months after randomisation, no survival difference was noted between the two groups (HR 1.09, 95% CI 0.51–2.32,  $p=0.82$ ). Thereafter, the 3-year survival rate was 89% in MPT patients and 70% in MP patients (HR 0.35, 95% CI 0.13–0.92,  $p=0.03$ ). The analysis of overall survival included data from 27 patients (21%) in the MP group who had disease progression and subsequently crossed over to receive thalidomide.

Grade 3–4 adverse events were reported in 62 (48%) MPT patients and in 32 (25%) MP patients ( $p=0.0002$ ) with an absolute difference of 22.7% (95% CI 12.8–31.9; table 3). In the MPT group, 11 deaths (8%) were reported as consequence of adverse events: cardiac failure (two patients), ventricular fibrillation (one), ventricular tachycardia (one), acute cardiac infarction (one), pneumonia (four), fever of unknown origin (one), and thromboembolism (one). In the MP group, six deaths from toxic effects (5%) were recorded as due to cardiac failure (three patients), ventricular tachycardia (one),

|                              | Number (%) patients |            | p*     |
|------------------------------|---------------------|------------|--------|
|                              | MPT (n=129)         | MP (n=126) |        |
| ≥1 event                     | 62 (48%)            | 32 (25%)   | 0.0002 |
| Haematological               | 29 (22%)            | 32 (25%)   | 0.59   |
| Neutropenia                  | 21 (16%)            | 22 (17%)   |        |
| Anaemia                      | 4 (3%)              | 5 (4%)     |        |
| Thrombocytopenia             | 4 (3%)              | 5 (4%)     |        |
| Thrombosis/embolism          | 15 (12%)            | 2 (2%)     | 0.001  |
| Deep-venous thrombosis       | 12 (9%)             | 2 (2%)     |        |
| Pulmonary embolism           | 3 (2%)              | 0 (0%)     |        |
| Neurological                 | 13 (10%)            | 1 (1%)     | 0.001  |
| Peripheral neuropathy        | 10 (8%)             | 0 (0%)     |        |
| Somnolence or fatigue        | 3 (3%)              | 1 (1%)     |        |
| Infective                    | 12 (10%)            | 2 (2%)     | 0.01   |
| Pneumonia                    | 6 (5%)              | 2 (2%)     |        |
| Fever of unknown origin      | 3 (2%)              | 0 (0%)     |        |
| Herpes zoster                | 1 (1%)              | 0 (0%)     |        |
| Upper respiratory            | 2 (2%)              | 0 (0%)     |        |
| Cardiac                      | 9 (7%)              | 5 (4%)     | 0.40   |
| Arrhythmia                   | 2 (2%)              | 1 (1%)     |        |
| Myocardial infarction/angina | 2 (2%)              | 0 (0%)     |        |
| Cardiac failure              | 4 (3%)              | 4 (3%)     |        |
| Hypertension                 | 1 (1%)              | 0 (0%)     |        |
| Gastrointestinal             | 8 (6%)              | 1 (1%)     | 0.036  |
| Constipation                 | 8 (6%)              | 0 (0%)     |        |
| Mucositis                    | 0 (0%)              | 1 (1%)     |        |
| Dermatological               | 4 (3%)              | 1 (1%)     | 0.37   |
| Rash                         | 3 (2%)              | 0 (0%)     |        |
| Toxic epidermal necrolysis   | 1 (1%)              | 1 (1%)     |        |
| Renal                        | 1 (1%)              | 0 (0%)     | 0.99   |
| Creatinine increase          | 1 (1%)              | 0 (0%)     |        |
| Oedema                       | 1 (1%)              | 0 (0%)     | 0.99   |
| Bleeding                     | 0 (0%)              | 1 (1%)     | 0.49   |

All grade 3–4 adverse events reported by patient or observed by investigator were reported. \*Proportions compared with  $\chi^2$  or Fisher's exact test.

**Table 3: Grade 3–4 adverse events**

and pneumonia (two). In the MPT group, the most frequent grade 3–4 adverse events were haematological (29 patients), thromboembolism (13), infections (12), and peripheral neuropathy (ten).

In the 65 patients who received MPT before the introduction of anticoagulant prophylaxis, grade 3–4 adverse events were reported in 37. In the 64 who received enoxaparin, grade 3–4 adverse events were observed in 25, the absolute difference between these two groups for all grade 3–4 adverse events was  $-18\%$  (95% CI  $-31.3$  to  $-3.3$ ) and the reduction was significant ( $p=0.042$ ). As a subgroup, thromboembolism only was significantly reduced ( $p=0.005$ ). In the MPT group, thromboembolism grade 3–4 was reported in 11 of 65 patients who did not receive anticoagulant prophylaxis (13 events were observed) and in two of 64 patients after the introduction of enoxaparin prophylaxis. These two patients had evidence of thromboembolism within 2 months after the discontinuation of enoxaparin. Grade 3–4 peripheral neuropathy was reported in ten MPT patients after a median of 8 months. Grade 2 peripheral neuropathy resulted in the reduction of the dose of thalidomide to 50 mg in 12 patients after a median of 5.8 months. Three of these patients subsequently discontinued the drug after a median of 1.9 months. In the MPT group, grade

3–4 infections included pneumonia (six patients), infection of upper respiratory tract (two), herpes zoster (one), and fever of unknown origin (three). These infections occurred within the first 4 months of treatment, and all patients in whom pneumonia was reported were older than 70 years. In the MPT group, grade 3–4 cardiac toxic effects were due to cardiac failure (four patients), ventricular fibrillation (one), ventricular tachycardia (one), myocardial infarction (two), and hypertension (one). Four of nine patients had pre-existing cardiac comorbidities, including mild dilatative cardiomyopathy (two), hypertensive cardiopathy (one), and atrial fibrillation (one). All grade 3–4 cardiac adverse events were observed in patients older than 70 years ( $p=0.03$ ).

## Discussion

Our findings show that the oral combination of melphalan, prednisone, and thalidomide is more effective than standard treatment for newly diagnosed multiple myeloma. This advantage was noted in patients older than 65 years and in younger patients who were unable to undergo transplantation. 50% of our patients were older than 72 years, and 25% were older than 75 years. However, this benefit must be balanced against increased rates of thromboembolism, neurological toxic effects, infection, and a short-follow-up.

Previous meta-analyses have shown that response rates were significantly higher with combination chemotherapy than with MP but there was no difference in remission duration and survival between the two groups.<sup>5</sup> Until now, autologous stem-cell transplantation was the only procedure that extends disease-free survival and overall survival in comparison with standard treatments.<sup>2–4</sup> In newly diagnosed patients, thalidomide has been used in combination with dexamethasone, with doxorubicin, or with melphalan, but few non-randomised trials have been published. A high response rate has been recorded generally, but very few data on progression-free survival have been reported.<sup>25,31,32</sup> This trial shows that the MPT combination significantly increases response rate, progression-free survival, and possibly survival, compared with MP.

In this study, the overall rate of complete response to oral MPT was 15.5%, nearly five times greater than that to MP alone. In another randomised trial, the rate of complete response after 12 courses of MPT with thalidomide given at the maximum tolerated dose of 400 mg per day, was 14%.<sup>33</sup> Our results compare favourably with the overall complete response rate of 10% reported with thalidomide and dexamethasone.<sup>25</sup> Event-free survival was significantly improved in the MPT group, compared with the MP group. It was increased by about 16 months in patients who received thalidomide, compared with those who did not. However, these results should be judged with caution, since the 95% CI of HR are rather wide.

In the MPT group, a higher proportion of early deaths from adverse events was reported in the first 9 months of treatment, compared with the MP group. This difference negatively affected early phases of overall survival in the MPT group. Thus in the intention-to-treat analysis, the survival advantage of the MPT group was not evident in the first 9 months after randomisation. Thereafter, a trend toward a survival advantage became evident. The incidence of early deaths might be reduced in patients younger than 80 years with normal cardiac and pulmonary functions, and with better management of side-effects with antibiotic and anticoagulant prophylaxis.

The MPT regimen was more effective than MP, but the rates of grade 3–4 adverse events were significantly higher. The major side-effects of thalidomide were consistent in type and frequency with those described previously.<sup>6,12–27</sup> The incidence of grade 3–4 adverse events was significantly reduced with the introduction of anticoagulant prophylaxis, and introduction of standard procedures adequately managed some adverse events. Enoxaparin prophylaxis<sup>34,35</sup> reduced the incidence of thromboembolism. Even though this comparison was not randomised, the large difference was unlikely to be due to pure chance or bias. In the 65 MPT patients without anticoagulant prophylaxis, thromboembolism was observed within the first 4 months of treatment. For these reasons, enoxaparin was instituted for a period of 4 months only. In two of 64 patients on anticoagulant prophylaxis, thromboembolism was observed within 2 months after discontinuation of enoxaparin.

In 12 patients, the dose of thalidomide maintenance therapy was reduced to 50 mg per day because of the occurrence of grade 2 peripheral neuropathy. In nine patients, symptoms stabilised or improved. In three patients, symptoms worsened and therapy had to be stopped. Evidence is now emerging that clinical response can be achieved at lower doses of 50 mg of thalidomide with minimal long-term toxic effects.<sup>36</sup> If these observations are confirmed in a larger series of patients, the dose of 50 mg per day should be considered for long-term maintenance use of the drug.

The incidence of infections was higher in patients receiving thalidomide, probably because of the drug's immunomodulatory effects. Pneumonias were the most frequent grade 3 adverse events. A more careful assessment of fevers of unknown origin and the prompt institution of antibiotic prophylaxis might reduce the incidence of these adverse events.

After 50 years of unsuccessful attempts to find new and more effective treatment approaches suitable for most patients with myeloma, our results lend support to the use of thalidomide in the initial treatment of elderly patients with multiple myeloma.

#### Italian Multiple Myeloma Network GIMEMA

In addition to the authors, the following investigators (listed in alphabetical order) participated in this study: Prof Aglietta, Divisione di Ematologia, Istituto di Ricerca e Cura del Cancro (IRCC), Candiolo;

Dr Amadori, Dipartimento di Oncoematologia, Ospedale Morgagni, Forlì; Prof Angelucci, Unità Operativa di Ematologia, Ospedale A Businco, Cagliari; Prof Annino, Divisione di Ematologia, Ospedale San Giovanni Addolorata, Roma; Dr Baraldi, Divisione di Ematologia, Azienda Ospedaliera “SS Antonio e Biagio e C Arrigo”, Alessandria; Dr Bazzan, Unità Operativa di Ematologia, Ospedale Evangelico Valdese, Torino; Dr Beggiato, Divisione di Medicina, Ospedale Civile, Ciriè; Dr Bongarzone, Divisione di Ematologia, Ospedale San Giovanni Addolorata, Roma; Prof Brugiattelli, Unità Operativa di Ematologia, Azienda Ospedaliera Papardo, Messina; Dr Capaldi, Divisione di Ematologia, IRCC, Candiolo; Dr Carubelli, Unità Operativa di Ematologia, Ospedale A Businco, Cagliari; Dr Castagna, Dipartimento di Oncoematologia Medica, Istituto Clinico Humanitas, Rozzano; Prof Dammacco, Sezione Medicina Interna e Oncologia Clinica, Policlinico, Bari; Prof Di Raimondo, Cattedra di Ematologia, Ospedale Ferrarotto, Catania; Dr Didino, Divisione di Medicina, Ospedale S S Trinità, Borgomanero; Prof Dore, Istituto di Ematologia, Università di Sassari, Sassari; Dr Elice, Divisione di Ematologia, Ospedale San Bortolo, Vicenza; Dr Ficara, Divisione di Medicina, Azienda Ospedaliera San Giovanni Battista, Ospedale S Vito, Torino; Dr Galliano, Oncologia Medica, ASL18, Alba; Prof Gallo, Ematologia, Azienda Ospedaliera San Giovanni Battista, Torino; Prof Giustolisi, Cattedra di Ematologia, Ospedale Ferrarotto, Catania; Dr Gottardi, UO Ematologia, Ospedale Maurizio Umberto I, Torino; Dr Griso, Divisione di Medicina, ASL 10, Pinerolo; Dr Guglielmelli, Divisione di Medicina Interna II, Ospedale San Luigi, Orbassano; Dr Lauta, Sezione Medicina Interna e Oncologia Clinica, Policlinico, Bari; Dr Levis, Divisione di Ematologia, Azienda Ospedaliera “SS Antonio e Biagio e C Arrigo”, Alessandria; Prof Longinotti, Istituto di Ematologia, Università di Sassari, Sassari; Dr Marinone, Divisione di Medicina Azienda Ospedaliera San Giovanni Battista, Ospedale S Vito, Torino; Dr Montanaro, Divisione di Ematologia, Ospedale Civile, Montefiascone; Dr Morandi, Unità di Ematologia, Azienda Istituti Ospitalieri, Cremona; Dr Nozza, Dipartimento di Oncoematologia Medica, Istituto Clinico Humanitas, Rozzano; Prof Petti, SC Ematologia, Ospedale Regina Elena, Roma; Dr Piro, Unità Operativa Ematologia, Azienda Ospedaliera Pugliese-Ciacco, Catanzaro; Dr Pisani, S C Ematologia, Ospedale Regina Elena, Roma; Prof Poccardi, U O Ematologia, Ospedale Maurizio Umberto I, Torino; Dr Pregno, Ematologia, Azienda Ospedaliera San Giovanni Battista, Torino; Dr Quartarone, Unità Operativa di Ematologia, Azienda Ospedaliera Papardo, Messina; Prof Rodeghiero, Divisione di Ematologia, Ospedale San Bortolo, Vicenza; Dr Ronconi, Dipartimento di Oncoematologia, Ospedale Morgagni, Forlì; Dr Rus, Unità Operativa di Ematologia, Ospedale Evangelico Valdese, Torino; Prof Saglio, Divisione di medicina Interna II, Ospedale San Luigi, Orbassano; Prof Semenzato, Divisione di Immunologia Clinica Universitaria, Dipartimento Medicina Clinica sperimentale, Padova; Dr Stefani, Divisione di Medicina, Ospedale S Spirito, Bra; Dr Zaccaria, Sezione di Ematologia, Ospedale Santa Maria delle Croci, Ravenna; Dr Zambello, Divisione di Immunologia Clinica Universitaria, Dipartimento Medicina Clinica Sperimentale, Padova.

#### Contributors

A Palumbo and M Boccardo designed the study, supervised its conduct and data analysis, and wrote the report. A M Liberati and P Musto coordinated the national study, and reviewed and commented on the draft of the report. S Bringhen, M T Ambrosini, I Avonto, and P Falco did the data analysis and assisted in writing the manuscript. M Ceccarelli and G Ciccone did the statistical analysis and reviewed the manuscript. T Caravita, E Merla, V Capparella, V Callea, C Cangialosi, M Grasso, F Rossini, M Galli, L Catalano, E Zamagni, M T Petrucci, and V De Stefano recruited patients.

#### Conflict of interest statement

A Palumbo and M Boccardo have received scientific adviser board and lecture fees from Pharmion and Celgene. Their association with Celgene involves lenalidomide only, and does not involve thalidomide. The other authors declare that they have no conflict of interest.

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