**Thalidomide-Dexamethasone compared to Melphalan-Prednisolone in elderly patients with Multiple Myeloma**

**Short title:** Thalidomide-Dexamethasone versus MP in myeloma

Heinz Ludwig¹, Roman Hajek², Elena Tóthová³, Johannes Drach⁴, Zdenek Adam², Boris Labar⁵, Miklós Egyed⁶, Ivan Spicka⁷, Heinz Gisslinger⁸, Richard Greil⁹, Ingrid Kuhn¹⁰, Niklas Zojer¹, Axel Hinke¹¹

¹Department of Medicine I, Wilhelminenspital Vienna, Austria, ²Internal Hematooncological Clinic, Faculty Hospital Brno and Faculty of Medicine MU Brno, Czech Republic, ³Clinic of Hematology, Faculty Hospital with Policlinic, Kosice, Slovakia, ⁴Department of Oncology, University Clinic Vienna, Austria, ⁵Clinical Hospital “Rebro”, Zagreb, Croatia, ⁶Department of Internal Medicine, Kaposi Mór Teaching Hospital, Kaposvár, Hungary, ⁷¹st Internal Clinic, Charles University Prague, Czech Republic, ⁸Department of Hematology, University Clinic Vienna, Austria, ⁹University Clinic Salzburg, Austria, ¹⁰Schering-Plough Inc, Traiskirchen, Austria, ¹¹WISP Research Institute, Langenfeld, Germany

**Correspondence:**

Heinz Ludwig, MD
Department of Medicine I, Center of Oncology and Hematology
Wilhelminenspital, Vienna, Austria
Phone: +431 49150 2101, Fax: +431 49150 2109
Heinz.ludwig@wienkav.at

**Scientific category:** Clinical trials and observations
Abstract

Thalidomide-dexamethasone (TD) has successfully been used for treatment of young patients with multiple myeloma (MM). We compared TD with melphalan-prednisolone (MP) as first line treatment in 289 elderly patients with MM. Patients were randomized to either thalidomide 200mg plus dexamethasone 40mg, days 1-4, and 15-18 on even cycles and on days 1-4 on odd cycles, during a 28-day cycle or to melphalan 0.25mg/kg and prednisolone 2mg/kg orally on days 1-4 during a 28 to 42 day cycle. For maintenance, patients achieving stable disease or better were randomized to either thalidomide 100mg daily and 3 MU interferon α-2b TIW or to 3 MU interferon α-2b TIW only, but results on this phase will only be presented after longer follow up. TD resulted in a higher proportion of complete and very good remissions (26% vs. 13%, P=0.0066) and overall responses (68% vs. 50%, P=0.0023) compared to MP. Time to progression (21.2 vs. 29.1 months, P=0.2), and progression-free survival was similar (16.7 vs. 20.7 months, P=0.1), but overall survival was significantly shorter in the TD group (41.5 vs. 49.4 months, P=0.024). Toxicity was higher with TD, particularly in patients above 75 years with poor performance status. TD yielded higher response rates, but was more toxic in older patients and was associated with shorter overall survival. The study is registered as NCT00205751 at ClinicalTrials.gov.
Introduction

Multiple myeloma is one of the most frequent hematologic cancers with an annual incidence of approximately 20,000 cases in the United States\(^1\) and 30,000 patients in Europe.\(^2\) Median survival is roughly 3.5 years with conventional therapy in usually less fit elderly patients and approximately 6.5 years in patients eligible for and treated with high dose therapy and autologous transplantation\(^3\). Survival rates have been constant over the last decades and have only very recently been improved.\(^3,4\) This coincided with increasing use of autologous transplantation and was seen in parallel with the introduction of thalidomide\(^5\), but already before the approval of bortezomib and lenalidomide. Thalidomide exerts pleiotropic functions including anti-angiogenic, anti-inflammatory, and immunomodulatory activities in vitro\(^6\) and substantial anti-myeloma action in patients with previously untreated\(^7\) or relapsed/refractory disease.\(^8\) Thalidomide in combination with dexamethasone resulted in high response rates in young and also in longer progression-free survival in patients with variable age (31-86 years), but also in more toxicity, than treatment with dexamethasone only.\(^9,10\) When novel drugs are not available, melphalan and prednisone (MP) still is used as standard regimen.\(^11\) Recent studies employed MP as backbone for combination therapy with each of the new drugs.\(^12-15\)

In the present investigation we evaluated the therapeutic potential and the toxicity of TD in comparison with MP as first line treatment of elderly patients with multiple myeloma not eligible for high dose therapy. In the second phase of the trial we compared thalidomide plus interferon \(\alpha\)-2b with interferon \(\alpha\)-2b alone as maintenance therapy, results of which will be presented after longer follow up.
Materials and Methods

Patients

Patients with previously untreated active multiple myeloma not eligible for autologous transplantation with Durie Salmon stage II and III and, if they met the criteria of high risk, with stage I were enrolled between August 1, 2001 and October 31, 2007. Reasons for being not eligible for transplantation were age above 65 years, or younger than age 65 but either with significant co-morbidity, insufficient stem cells or due to patient’s decision. Patients were treated in 26 centers in Austria, Czech Republic, Slovakia, Hungary and Croatia and must have presented with adequate bone marrow (WBC ≥3,000/μl, platelets ≥100,000/μl) and hepatic function (SGOT, SGPT, and alkaline phosphatase <3 x upper limit of normal), with ECOG performance status of 3 or better and with a clear requirement for treatment, meaning that patients needed to be symptomatic from bone pain, and/or present with anemia (Hb<10g/dl), impaired renal function (creatinine >2.0mg/dl), or hypercalcemia (Ca >10.5mg/l). Patients with extramedullary or solitary plasmacytoma without evidence of dissemination of disease or with smouldering myeloma, with more than 3 irradiation fields, congestive heart failure (NYHA III and IV), acute infection, uncontrolled medical condition (e.g. diabetes, or glaucoma) were excluded. The study has been approved by the ethical committees responsible for the participating study centers. All patients gave written informed consent before entering the study, which was done in accordance with the declaration of Helsinki.
Study design and procedures

The study design comprised an induction and a maintenance phase. After registration in a centralised database, patients were randomly assigned to treatment. Patients were stratified according to Durie Salmon stage, type of M-component, creatinine concentration (≤2mg/dl vs. >2mg/dl) and study center using a centralized and computerized randomization system. For induction therapy, patients received either melphalan 0.25mg/kg and prednisolone 2mg/kg orally on days 1-4 during a 28 to 42 day cycle or thalidomide 50-400mg daily and dexamethasone 40mg on days 1-4 and 15-18 on even cycles, and on days 1-4 on odd cycles, during a 28-day cycle. The duration of cycles could be extended to 6 weeks if required for resolution of toxicity. Patients were scheduled to receive a total of 9 induction cycles, but patients with ≥VGPR could be stopped earlier, namely after administration of additional 3 cycles after the ascertainment of ≥VGPR. Investigators were encouraged to increase the dose of thalidomide up to 400mg, if tolerated well by patients. Thalidomide was provided by Grünenthal GmbH, Aachen, Germany, for Austria, Slovakia and Croatia, and by Lipomed AG, Arlesheim, Switzerland, for Czech Republic and Hungary. Patients who achieved stable disease or better, underwent a second randomization to maintenance therapy consisting of either 100mg thalidomide daily and 3Mio U interferon α-2b (Schering-Plough) TIW, or to 3Mio U interferon α-2b TIW. Patients were stratified by remission status, primary treatment and treatment center. All patients were scheduled to receive 4mg zoletronic acid (Novartis AG, Basel, Switzerland) in 4 weekly intervals continuously. After notifying an increased incidence
of thromboembolic complications in the first 49 patients treated with TD, an amendment was issued making prophylaxis with LMWH mandatory.

The primary objective was to compare progression-free survival and tolerance of both regimens and the secondary objective was to evaluate response rates, time to response and overall survival during both treatments. In addition, the effect of thalidomide in addition to interferon maintenance should be evaluated.

### Assessments

At inclusion, baseline assessments included standard haematological and chemistry analysis plus bone marrow biopsy and aspiration. In the induction phase, visits were planned every 4 weeks. Response assessment included measurement of serum paraprotein calculated by multiplying the proportion of monoclonal protein in the serum electrophoresis with the total protein level or in case of baseline paraprotein concentrations of less than 0.2g/dL by immunological techniques. In addition, 24-hour urine paraprotein excretion was determined. Immunofixation (IF) was used to identify IF negative complete response. Radiological investigations were performed as needed, and per protocol scheduled after termination of induction therapy and before enrolment into maintenance treatment. At this time a bone marrow biopsy and aspiration was repeated.

For evaluation of response, the EBMT criteria\textsuperscript{16} plus an additional category of very good partial response were used. In short, a complete response required disappearance of myeloma protein in serum and urine by immunofixation maintained for a minimum of 6 weeks, <5% plasma cells in bone marrow, no increase in lytic
bone lesions and disappearance of soft tissue plasmacytomas. Very good partial response required a serum and urine M-component detectable by immunofixation but not on electrophoresis or a 90% or greater reduction in serum M-component plus urine M-component <100 mg per 24 hours. A partial response needed a more than 50% reduction in the concentration of serum monoclonal protein, and/or more than 90% decrease in 24-hour urinary paraprotein reduction, or to <200mg, maintained for a minimum of 6 weeks, >50% reduction in plasma cells and/or of soft tissue plasmacytomas and no increase in lytic bone lesions. Minor response was defined as more than 25% and/or less than a 50% reduction in serum paraprotein or a more than 50%, but less than a 90% reduction in 24-hour urinary paraprotein excretion, which still exceeds 200mg/24hours, maintained for a minimum of 6 weeks, a 25-49% reduction in plasma cells and/or of soft tissue plasmacytomas and no increase in lytic bone lesions. Stable disease did not meet criteria of either minimal response or progressive disease. Progressive disease required at least one of the following: a greater than 25% increase in serum paraprotein concentration with an absolute increase of at least 5g/dl, a greater than 25% increase in 24-hour urinary paraprotein excretion with an absolute increase of more than 200mg confirmed by at least one repeated investigation, a >25% increase in plasma cells with an absolute increase of ≥10%, progressive bone disease or increase in size or development of new soft tissue plasmacytoma, hypercalcemia not attributable to other causes than myeloma. Best response was defined as the highest amount of disease improvement achieved by a patient at any visit from start of therapy to end of induction treatment.

Time to progression was calculated from the time of start of therapy to the time of progression of disease or death owing to progression of myeloma, while progression-
free survival was calculated from the time of start of therapy to the time of progressive
disease or to death of any cause. Overall survival was calculated from the time of
start of therapy until the date of death for any cause or the date the patient was last
known to be alive.

Adverse events were assessed at each visit and graded according to the National
Cancer Institute common toxicity criteria. Causes of death were recorded as
attributable to myeloma, infection, cardiovascular complications, other or unknown.
Myeloma related mortality was defined as death in patients fulfilling the criteria of
progressive disease. In those patients the final cause of death could be a combination
of progressive myeloma and cardiopulmonary, renal or bone marrow failure, infection
including sepsis or hypercalcemia. Thromboembolism was assessed by clinically
objective evidence of thrombosis and by ultrasound and, if indicated, by pulmonary
CT scan.

**Statistical analysis**

The trial was originally designed to significantly detect a suspected superiority in
progression-free survival (PFS) after 12 months of 65% vs. 50% of the standard MP
regimen over the innovative chemotherapy-free regimen with a power of 85% and a
one-sided alpha-error level of 0.025, requiring a total number of 194 evaluable
patients. The actually recruited number of cases is considerably higher, since more
patients had been required in order to achieve a power of 80% for the second
randomization of the trial, evaluating maintenance treatment. This resulted in an
increase in power for the induction phase to about 95%.
Response and toxicity rates and counts were analyzed by Fisher’s exact, Cochran-Armitage trend or Wilcoxon tests, as appropriate. Progression-free and overall survival, time to response, thrombotic events over time as well as time to early death were estimated by the product limit method. Univariate comparisons of these endpoints were performed using the logrank test. The Cox proportional hazard model was applied for multivariate analyses of event-type data and logistic regression for early non myeloma-related mortality. In both model types a stepwise backward model reduction after initially including all univariately significant characteristics was implemented. All P values reported are two-sided. Except for the primary endpoint, all statistical tests are of exploratory nature and no adjustments for multiplicity were applied. Subgroup analyses and analysis of thrombotic events, time to early non-myeloma related death in the TD group, outcome in different age groups were not pre-specified prospectively.

Results

Patient characteristics
Baseline patient characteristics were well balanced between both treatment groups with the exception of a tendency for a higher proportion of patients older than 70 years and with performance status of 2 or greater in the TD group (table 1).

Response rates and time to response
Thalidomide-dexamethasone (TD) resulted in a similar rate of complete responses (2% vs. 2%, P=1.0), but a significantly higher rate of very good partial responses (24% vs. 11%, P=0.0043) yielding a significantly higher proportion of patients with CR
and VGPR (26% vs. 13%, P=0.0066). Partial responses were observed in 42% of patients in the TD and in 37% of patients in the melphalan-prednisolone (MP) group. The respective figures for MR were 12% and 22% respectively. Overall response rate was significantly higher during therapy with TD (68% vs. 50%, P=0.0023). Median time to response and median time to best response was significantly shorter with TD compared to MP induction therapy (6 (range: 2-51) vs. 10 (range: 1-47), P<0.0001) and 12 (range: 2-51) vs. 20 (range: 4-74) weeks, P<0.0001 and P<0.0001, respectively).

**Time to progression and progression-free survival**

The median duration of follow-up from start of diagnosis was 28.1 months (range 1 – 70 months). Progression of disease or death was noted in 84 (59.2%) of patients on TD and in 72 (51.1%) of patients on MP. The median time to progression (figure 2A) was 21.2 months in the TD and 29.1 months in the MP group (HR: 1.26, CI: 0.88-1.80, logrank test P=0.2). Median progression free survival (figure 2B) was 16.7 months and 20.7 months in the respective groups (HR: 1.30, CI: 0.95-1.78, logrank test P=0.10). The estimated progression-free survival at 12 and 24 months respectively, was 59% (CI: 51%-68%) and 41% (CI: 33%-51%) in patients on TD and 63% (CI: 55%-72%) and 48% months (CI: 40%-58%) in those treated with MP.

**Overall survival**

Median overall survival was 41.5 months in patients treated with TD and 49.4 months in patients treated with MP (HR: 1.55, CI 1.06-2.27, logrank test, P=0.024) (figure 2C). The estimated overall survival at 12 and 24 months respectively, was 69% (CI:
62%-78%) and 61% (CI: 52%-70%) in patients on TD and 83% (CI: 77%-90%) and 70% (CI: 62%-79%) in those treated with MP.

Overall survival was significantly shorter in the entire group of patients aged >75 years compared to younger patients (≤75 years of age) (median: 25.3 vs. 49.4 months, P=0.002) (figure 3A). Overall survival tended to be shorter with TD in patients ≤75 years of age (median: 44.6 vs. 57.9 months, P=0.14) (figure 3B), but was markedly albeit not significantly shorter in TD treated patients older than (median: 19.8 vs. 41.3 months, P=0.071) (figure 3C).

**Number and causes of deaths**

At time of analysis 111 patients had died. The number of deaths was slightly and that of early deaths within the first year was significantly higher in patients treated with TD (64 (45%) vs. 47 (33%), P=0.051, and 40 (28%) vs. 22 (16%), P=0.014, respectively). 24 of the early deaths observed in the TD and 12 documented in the MP group occurred within the first six months (P=0.048).

25 of the 40 patients in the TD arm who died within the first year, died due to non-myeloma related causes (infection 12, cardiovascular 9, unknown 2, second cancer 1, ileus 1). In the MP group, 14 of the 22 patients died due to non-myeloma related causes (infection 6, cardiovascular 4, second cancer 1, ileus 1, renal failure 1, bleeding 1). Myeloma related mortality within the first 12 months was slightly, but not significantly higher in patients on TD (figure 4A). There were 75/214 (35%) deaths in patients ≤75 years and 36/69 (52%) deaths in patients >75 years. Causes of death were myeloma, infection, cardiovascular, and other/unknown in 42 (19.6%), 17
(7.9%), 10 (4.8%), 6 (2.8%) in the younger and 21 (30.4%), 6 (8.7%), 6 (8.7%) and 3 (4.3%) respectively, in the older group. After the first 12 months of therapy mortality did not differ between patients initially randomized to TD (24 (16.9%) or to MP (25, 17.7%), p=0.876). Likewise, there was no difference in the number of deaths between patients on higher (≥ 300mg/day) or lower doses of thalidomide within the first two cycles (15 (11%) vs. 21 (15%), p=0.372) and during the entire duration of thalidomide induction therapy (36 (25%) vs. 28 (20%), p=0.320). After progression, median time to death was significantly shorter in patients pre-treated with TD compared to the MP group (median: 3 vs. 6.7 months, logrank test: P=0.036) (figure 4B).

Predictors of early non-myeloma related mortality in patients treated with TD and in the entire patient cohort

Univariate analysis revealed low serum albumin (<3.5mg/dL) and poor ECOG performance status (2-3) as significantly associated with non-myeloma related early mortality in patients treated with TD (P=0.017 and P=0.0014, respectively). The multivariate analysis including variables associated with a P value of at least <0.5 (age, stage, creatinine, performance status, haemoglobin, albumin and center confirmed poor performance status (odds ratio: 7.6, CI: 2.35 – 24.5) followed by low albumin (odds ratio: 5.9, CI: 1.75-20.0) as independent significant predictors for early non-myeloma related mortality. Multivariate analysis in the entire cohort of 283 patients employing age, performance status and treatment arm confirmed TD as independent predictor for shortened first year survival (odds ratio: 1.95, CI 1.06-3.60, p=0.032). Age (odds ratio 2.59, CI: 1.41-4.75, p=0.0021) and poor performance status (odds ratio: 3.02, CI 1.65-5.56) retained their negative prognostic impact.
Number of cycles and dose of thalidomide

At time of data closure, two thirds of the patients (TD: 65% and MP: 68%) had already received the planned 9 cycles of either therapy. Investigators were asked to start treatment with 200mg thalidomide daily and to increase the dose if possible to 400mg. Information was available in 136 (94%) of the 145 patients randomized to TD. At cycle 2, 35% of the patients received 400mg. The proportion of patients on this dose gradually declined to 28% at cycle 9. The mean percentage of patients with daily doses of 300, 200, 100 and 50mg was rather constant throughout cycles 2-9 and amounted to 16%, 36%, 17%, and 4%, respectively. The median cumulative dose of thalidomide was 42 grams (range: 1.4 - 162.4 grams) yielding a median daily dose of 200mg (range 50 - 400mg). Patients were on average 200 days on TD therapy. Comparison of a higher dose of thalidomide (≥300mg) with a lower dose (≤200mg) did not reveal a significant difference in response rates, progression-free survival, survival and early non-myeloma related mortality (P=0.39, P=0.58, P=0.70, P=0.65, respectively).

Maintenance treatment

Of the 111 patients enrolled into the maintenance phase, 54 have been randomized to thalidomide-interferon α-2b and 57 to interferon α-2b maintenance therapy. Median duration of maintenance therapy was 9.9 months and median follow-up of these patients was 17.2 months. Median survival from start of maintenance treatment was 53.1 months in patients randomized to thalidomide-interferon α-2b maintenance therapy, while the median has not been reached as yet in patients on interferon α-2b maintenance only (logrank test, P=0.49). When survival after start of maintenance
was analysed in relation to the induction treatment, no difference was observed (TD: median 41.1 months, MP: median 53.1 months, P=0.41).

**Toxicity**

Grade 3-4 leukopenia and thrombopenia was more frequently reported in patients in the MP group (15% vs. 3%, P<0.001, and 12% vs. 1%, P<0.001, respectively) while for neuropathy, constipation and psychological disturbances, a significant trend for greater toxicity during TD therapy was observed (P<0.0001, P<0.0002, and P<0.0013, respectively) (table 2).

Thromboembolic events have been documented in 17 patients in the TD and 9 cases in the MP arm (P=0.15), within the first year. 13 patients presented with deep vein thrombosis (DVT) in the former, and in 5 patients in the latter treatment group; pulmonary embolism was seen in 4 patients of each treatment arm. Within the first 2 months after start of therapy, thromboembolic complications occurred in 8 patients of the TD and in 3 of the MP group (figure 4C). The cumulative incidence rate was 15% in the TD and 8% in the MP group. After enrolment of 48 patients to TD, prophylaxis for thromboembolic complications with LMW heparin was recommended for the first 6 months of TD treatment in February 2004. This resulted in a 35% relative risk reduction of thromboembolic complications within the first 6 months of TD therapy from actually 12.4% to 9%.

Osteonecrosis of the jaw occurred in 2 patients, 14 and 34 months after enrolment, both had been on maintenance therapy with thalidomide-interferon α-2b after MP induction therapies.
Discussion

This is the first trial comparing TD with MP in elderly patients. Results in the TD group showed a significantly higher rate of very good responses (CR and VGPR) and significantly shorter time to response with no difference in time to progression (figure 2A), progression-free survival (figure 2B). Surprisingly, overall survival, however, was found to be significantly shorter with TD therapy (figure 2C). Response rates obtained with TD in this trial were similar to those reported with this regimen by other groups. In these studies younger patients had been enrolled and survival data were either not reported, or influenced by subsequent autologous stem cell transplantation leaving our trial as the only one reporting survival as main consequence of conventional therapy. The data also indicate that significant tumor reduction does not always translate into better outcome, a phenomenon observed in some other studies as well. This seems to be more common with high dose dexamethasone containing regimen and may partly be due to a ‘cosmetic effect’ with greater reduction in M-component concentration than in myeloma cells, as well as because of greater toxicity and significant immunosuppression by cortisone induced apoptosis of immune cells. In accordance with these considerations, high dose continuous corticosteroid therapy has also been shown to have a detrimental effect on survival in certain non-hematologic malignancies.

The progression-free and overall survival observed in this study is in the range of results obtained in recent trials comparing MPT with MP. Based on the poorer survival with TD particularly in the elderly patients, one may argue that thalidomide in
combination with MP offers a valuable alternative to TD because it exploits the advantage of the traditional MP regimen that showed remarkable activity also in the present study. MPT avoids the significant toxicity of high dose dexamethasone, although it may also induce considerable toxicity, particularly in patients older than 75 years, but renders high response rates and long progression-free survival. Overall survival with MPT, however, was only found to be superior to MP in two out of the five randomized trials presented so far.

Expectedly, in the entire cohort, overall survival was significantly shorter in patients >75 years of age (figure 3A). TD resulted in a trend for lower survival rates compared to MP in patients of age 75 or younger (figure 3B), but showed a marked, although not significant tendency for shorter survival in patients above this age, partly because of increased toxicity (figure 3C). During the first 12 months of therapy, almost double as many patients died due to non-myeloma related causes in the TD group compared to the MP arm. Multivariate analysis revealed poor ECOG performance status (2-3) followed by low serum albumin as the most important predictors of early non-myeloma related mortality. Frequent causes of early non-myeloma related mortality were infections in 12 and cardiovascular toxicity in 9 of the 25 patients dying due to other causes than myeloma during the first year. The independent prognostic impact of TD therapy for shortened survival within the first 12 months of treatment was also confirmed by multivariate analysis including all 283 patients.

The median dose of thalidomide was 200mg per day in individual patients with dose adaptations ranging from 50mg to 400mg per day resulting in approximately 20% of patients receiving 100mg or less, 36% receiving 200mg and the other patients being
treated with 300-400mg. The design of the trial which stems from 2001, required investigators to aim for a thalidomide dose of 400mg per day, a policy which later has been abandoned in clinical practice, because subsequent studies found lower doses similarly effective but better tolerable.\textsuperscript{7}

Maintenance therapy with thalidomide-interferon $\alpha$-2b yielded similar survival data than treatment with interferon $\alpha$-2b only. Since we used sequential randomization, half of the patients enrolled into the maintenance phase had already been pretreated with TD, which might explain the similar outcome in survival in both maintenance groups. Presently, comparisons of this part of the study are hampered by the low number of events; therefore we plan to report on this phase of the trial after longer follow-up. Use of interferon may partly account for the rather long overall survival observed in both groups, given the high age of the patients. Previously, two meta-analyses have shown a survival gain of half a year with interferon maintenance therapy.\textsuperscript{27,28} Time from progression to death was relatively short with 6.7 months in patients induced with MP and only 3 months in those initially started with TD (figure 4B). Although we are not able to provide the exact number of patients that have received bortezomib or lenalidomide for second or later line therapy, only around 10% had access to the proteasome inhibitor and less than 5% to the newer IMiD. Maintenance treatment with interferon has previously been associated with short post progression survival,\textsuperscript{29} a phenomenon that may also have contributed to the unfavourable outcome after relapse. The significantly shorter survival after progression of disease in patients pre-treated with TD (figure 4B) is of particular interest. Analogous findings have already previously been reported by Barlogie in patients receiving thalidomide during upfront and-maintenance phase in conjunction.
with autologous transplantation. These authors noticed a more than 50% reduction in post relapse survival and a higher proportion of drug resistant patients after thalidomide treatment. Palumbo reported similar findings in patients treated with MPT in comparison to MP. In this study, survival from relapse was less than half in the group with prior thalidomide therapy, indicating again that prolonged exposure to thalidomide may either induce a more malignant myeloma phenotype and/or alter the bone marrow stroma and/or the immune system in a direction favouring proliferation of myeloma cells.

The toxicities previously associated with thalidomide-based combinations were also observed in this trial. Neuropathy, constipation and psychological disturbances were significantly more frequent as well as thromboembolic complications. The latter occurred primarily during the first months after start of therapy and were only partly reduced after the introduction of low molecular weight heparin prophylaxis (figure 4C). Severe complications resulting in non-myeloma related mortality were probably primarily due to high dose dexamethasone and most likely not a consequence of the high starting dose of thalidomide, since mortality did not differ between patients on higher (≥300mg) and lower doses (≤200mg) of thalidomide. Mortality was significantly associated with poor performance status and predominantly seen in patients >75 years of age. This observation has significant implications for clinical practice: Elderly patients with poor performance status should not be started on high dose dexamethasone in combination with thalidomide. In those patients a less aggressive approach with lower doses of dexamethasone and thalidomide or thalidomide in combination with melphalan-prednisone seems to be a more appropriate treatment strategy.
In conclusion, TD resulted in higher remission rates and in shorter time to response than MP, but led to higher one year mortality and significantly shorter overall survival.

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Authorship
Contributions: Heinz Ludwig designed the study, served as principal investigator, organized study group meetings and wrote the manuscript. Roman Hajek, Elena Tóthová, Johannes Drach, Zdenek Adam, Boris Labar, Miklós Egyed, Ivan Spicka, Heinz Gisslinger, Richard Greil and Niklas Zojer served as investigator and contributed patient data, participated in study group meetings and commented on the final analysis and the manuscript. Ingrid Kuhn provided organisational support, participated in study group meetings and commented on the final analysis and the manuscript. Axel Hinke conducted the statistical analysis, participated in study group meetings and commented on the final analysis and the manuscript. All authors had access to primary clinical trial data.
Conflict of interest statements: The authors declare no conflict of interest.

Contributors: The following members of the Central European Myeloma Study Group (CEMSG) contributed by treating patients within the study and providing data:

**Austria:** Werner Linkesch (University Clinic Graz), Josef Thaler (Klinikum Kreuzschwestern Wels), Thomas Kühr (Klinikum Kreuzschwestern Wels), Alois Lang (LKH Feldkirch), Johannes Schüller (Rudolfstiftung Vienna), Gunther Gastl (University Clinic Innsbruck), Richard Haidinger (LKH Steyr), Werner Lin (LKH Villach), Regina Reisner (Hanuschkrankenhaus Vienna), Hedwig Kasparu (A.ö. Krankenhaus der Elisabethinen Linz). **Czech Republic:** Vlastimil Scudla (Faculty Hospital Olomouc), Jaromir Gumulec (J.G. Mendel Cancer Center, Novy Jicin), Evzen Gregora. (Fac Hospital Kralovske Vinohrady, Prague). **Slovakia:** Martin Mistrik (Hospital of St. Cyril and Method, Bratislava). **Croatia:** Branimir Jaksic (Kl. Krank. Merkur, Zagreb), Rajko Kusec (Kl. Krank. Merkur, Zagreb). **Hungary:** Gábor Tarkovács (Semmelweis University Medical School, Budapest), Tamás Masszi (Szent László Hospital, Budapest).
References


Table 1. Patient characteristics

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<tr>
<th>Parameter</th>
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<th>MP</th>
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<td>Number of Patients</td>
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<td><strong>Age</strong>, Median (range)</td>
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<td>72 (55-86)</td>
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<td>≥ 80 yrs.</td>
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<td>27 (19%)**</td>
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<td></td>
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<tr>
<td>IgG</td>
<td>91 (62.7%)</td>
<td>94 (65.7%)</td>
</tr>
<tr>
<td>IgA</td>
<td>33 (22.7%)</td>
<td>32 (22.4%)</td>
</tr>
<tr>
<td>Light Chain</td>
<td>17 (11.7%)</td>
<td>15 (10.5%)</td>
</tr>
<tr>
<td>IgD</td>
<td>4 (2.7%)</td>
<td>2 (1.4%)</td>
</tr>
<tr>
<td><strong>Bone marrow plasma cell infiltration</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 234</td>
<td>122</td>
<td>112</td>
</tr>
<tr>
<td>Median (range)</td>
<td>22 (4-90)</td>
<td>25 (5-91)</td>
</tr>
<tr>
<td><strong>Hemoglobin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 264</td>
<td>133</td>
<td>131</td>
</tr>
<tr>
<td>Median (range [g/dl])</td>
<td>10.8 (6.0-15.2)</td>
<td>10.8 (2.9-15.4)</td>
</tr>
</tbody>
</table>
### β2-microglobulin

<table>
<thead>
<tr>
<th></th>
<th>N = 245</th>
<th>Median (range [mg/l])</th>
<th>≤3.5mg/l</th>
<th>&gt;3.5mg/l</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>122</td>
<td>50 (41%)</td>
<td>72 (59%)</td>
</tr>
<tr>
<td><strong>P=0.123</strong></td>
<td></td>
<td>123</td>
<td>56 (46%)</td>
<td>67 (54%)</td>
</tr>
</tbody>
</table>

### Albumin

<table>
<thead>
<tr>
<th></th>
<th>N = 251</th>
<th>Median (range [g/l])</th>
<th>≤35g/l</th>
<th>&gt;35g/l</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>125</td>
<td>55 (44%)</td>
<td>70 (56%)</td>
</tr>
<tr>
<td><strong>P=0.123</strong></td>
<td></td>
<td>126</td>
<td>31 (25%)</td>
<td>95 (75%)</td>
</tr>
</tbody>
</table>

### Creatinine

<table>
<thead>
<tr>
<th></th>
<th>N = 250</th>
<th>Median (range [mg/l])</th>
<th>128</th>
<th>122</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>11 (0.57-8.05)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Calcium

<table>
<thead>
<tr>
<th></th>
<th>N = 241</th>
<th>Median (range [mmol/l])</th>
<th>122</th>
<th>119</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2.31 (1.56-3.62)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* excluding a patient with randomization failure, **P=0.123
Table 2. Adverse events graded according the National Cancer Institute toxicity criteria.

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Number (%) of Patients</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TD (n=134)</td>
<td>MP (n=134)</td>
</tr>
<tr>
<td><strong>Hematological</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>6 (4%)</td>
<td>15 (11%)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>4 (3%)</td>
<td>20 (15%)</td>
</tr>
<tr>
<td>Thrombopenia</td>
<td>2 (1%)</td>
<td>16 (12%)</td>
</tr>
<tr>
<td>Infection</td>
<td>18 (13%)</td>
<td>11 (8%)</td>
</tr>
<tr>
<td><strong>Thromboembolic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT</td>
<td>13 (10%)</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>4 (3%)</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15 (11%)</td>
<td>8 (6%)</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>10 (7%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Neuropathy (G1+2)</td>
<td>87 (65%)</td>
<td>43 (32%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>10 (7%)</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>Constipation (G1+2)</td>
<td>35 (26%)</td>
<td>13 (10%)</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>8 (6%)</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>Renal (Creatinine increase)</td>
<td>6 (4%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td><strong>Pulmonary</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>4 (3%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>4 (3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Cardiac</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiotoxicity</td>
<td>4 (3%)</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Edema</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>
### Skin

<table>
<thead>
<tr>
<th>Condition</th>
<th>Group A</th>
<th>Group B</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exanthema/Rash</td>
<td>2 (1%)</td>
<td>2 (1%)</td>
<td>= 1.0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>2 (1%)</td>
<td>0 (0%)</td>
<td>= 0.498</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>2 (1%)</td>
<td>0 (0%)</td>
<td>= 0.498</td>
</tr>
<tr>
<td>Psychological disturbance</td>
<td>2 (1%)</td>
<td>1 (1%)</td>
<td>&lt; 0.0013*</td>
</tr>
<tr>
<td>Psych. Dist. (G1+2)</td>
<td>48 (36%)</td>
<td>24 (18%)</td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>= 1.0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>= 1.0</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>= 1.0</td>
</tr>
<tr>
<td>Reported grade 3-4 events</td>
<td>121</td>
<td>104</td>
<td></td>
</tr>
</tbody>
</table>

*Cochrane-Armitage trend test*
Figure Legends

Figure 1. Study flow chart

Figure 2. **Survival times** A. Time to progression from entry into the trial in patients treated with thalidomide-dexamethasone or melphalan-prednisolone B. Progression-free survival from entry into the trial by treatment and C. Overall survival from entry into the trial by treatment

Figure 3. **Overall survival by age group**. A. Overall survival by treatment in patients of age 75 years or younger and in those older than 75 years. B. Overall survival in patients of age 75 years or younger by treatment. C. Overall survival in patients older than 75 years by treatment.

Figure 4. **Time to early death, time from progression to death, and time to thromboembolic event**. A. Time to early death (within 12 months after entry into the trial) due to all causes or due to non-myeloma related causes by treatment. B. Time from progression to death by treatment. C. Time to thromboembolic event by treatment.
Figure 1.

289 Patients randomized

145 assigned to TD
- 3 too early

142 Intent to treat population
- 7 early deaths
- 4 exclusions due to SAE's
- 1 early cancer
- 4 withdrawals of consent
- 3 other

123 per protocol population

144 assigned to MP
- 1 too early
- 1 no data
- 1 randomization failure

141 Intent to treat population
- 6 early deaths
- 3 exclusions due to SAE's
- 2 protocol violation
- 3 withdrawals of consent
- 1 no data

126 per protocol population
Figure 2

A Time to Progression by Therapy

B Progression-free Survival by Therapy

C Overall Survival by Therapy
Figure 3

A  Overall Survival by age Group

B  Overall Survival in Patients of age ≤ 75 years by Treatment

C  Overall Survival in Patients of age older than 75 years by Treatment
Figure 4

A  Time to Early Death, by Treatment

B  Time from Progression to Death, by Treatment

C  Time to Thromboembolic Event, by Treatment
Thalidomide-dexamethasone compared to melphalan-prednisolone in elderly patients with multiple myeloma

Heinz Ludwig, Roman Hajek, Elena Tothova, Johannes Drach, Zdenek Adam, Boris Labar, Miklos Egyed, Ivan Spicka, Heinz Gisslinger, Richard Greil, Ingrid Kuhn, Niklas Zojer and Axel Hinke