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ORIGINAL ARTICLE

Melphalan and prednisone versus melphalan, prednisone and thalidomide for elderly and/or transplant ineligible patients with multiple myeloma: a meta-analysis

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Trials comparing efficacy of melphalan prednisone (MP) with MP plus thalidomide in transplant ineligible, elderly patients with multiple myeloma have provided conflicting evidence. Although there is agreement regarding improved response rates (RRs) and higher toxicity with the addition of thalidomide to MP, the impact on progression free survival (PFS) and overall survival (OS) is less clear. We performed a meta-analysis comparing efficacy of melphalan, prednisone and thalidomide (MPT) and MP by pooling results on RR, PFS and OS reported in all the identified randomized controlled trials (RCTs) under a random effects model. Overall, six prospective RCTs, with data extractable from five published trials ($n=1568$) were identified. The pooled odds ratio of responding to therapy with MPT vs MP was 3.39 ($P<0.001$, 95% CI: 2.24–5.12). The pooled hazard ratios for PFS and OS were and 0.68 ($P<0.001$; 95% CI: 0.55–0.82) and 0.80 ($P=0.07$; 95% CI: 0.63–1.02), respectively, in favor of MPT. The odds ratios for high grade peripheral neuropathy and deep venous thrombosis were 6.6 and 2.4, respectively, in favour of MP. There was significant heterogeneity among the RCTs. Our meta-analysis demonstrates that in previously untreated, transplant ineligible, elderly myeloma patients, the addition of T to MP results in significantly improved RR and PFS with a trend towards improvement in OS compared with MP alone, but at a cost of significantly greater toxicity.
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Introduction

The introduction of novel agents thalidomide, lenalidomide and bortezomib over the last decade has transformed the therapy for multiple myeloma (MM). Although a major focus of clinical investigation currently is to improve upon overall response rates (RRs) and eventually long-term control by assessing the efficacy of various front-line novel-agent combination regimens such as bortezomib, thalidomide, dexamethasone (VTD), bortezomib melphalan prednisone, thalidomide (VMPT) and bortezomib cyclophosphamide, lenalidomide and dexamethasone (VCRD), it is becoming increasingly clear that addition of an individual novel agent (thalidomide, lenalidomide or bortezomib) to traditional MP regimen could be synergistic and influence the disease outcome. Emergence of multiple active combination regimens has led to expansion of the management strategies. Consequently, the appropriateness of the use and tolerability of such regimens in different patient populations is another area of active research interest among investigators.

Nearly two-thirds of patients with MM are older than 65 years of age.[1] Evidence from many single-institution experiences has suggested similar survival benefit for transplant eligible, elderly patients when compared with their younger counterparts.[2–4] However, in general, the options for the elderly are fewer, particularly for those with poor functional status and co-morbid illnesses who are unfit to undergo transplantation. In addition, chronological age of 65 years is used as cut-off for autologous stem cell transplantation (ASCT) in Europe.[5] Trials comparing efficacy of standard MP therapy with MP plus thalidomide in transplant ineligible or elderly patients with MM have provided conflicting evidence.[6–10] Although there is greater agreement with regard to superior RRs with the addition of thalidomide to MP in elderly/transplant ineligible patients, the impact on progression free survival (PFS) and overall survival (OS) is less clear with some trials demonstrating an improvement in PFS and/or OS with melphalan, prednisone and thalidomide (MPT) and others showing no difference in outcomes.[6–10] We performed a systematic review to integrate the existing outcome data related to the efficacy of MP vs MPT using a meta-analytic approach.

Methods

We used comprehensive strategies to identify potentially relevant randomized controlled trials (RCTs) through June 15th 2010. The published RCTs were searched through electronic databases (MEDLINE, EMBASE, Cancerlit) without language restrictions using the Cochrane collaboration optimal search strategy.

This was supplemented by manual searches of abstracts presented at the American Society of Hematology (ASH), American Society of Clinical Oncology (ASCO), European Hematology Association (EHA) and International Myeloma Foundation meetings in addition to the reference lists of the retrieved articles. We included only the prospective RCTs comparing MP with MPT in previously untreated elderly and/or transplant ineligible patients with MM that reported RR, progression-free or event-free survival (PFS/EFS), OS and treatment-related adverse effects on an intention-to-treat basis. The methodological quality of studies was rigorously assessed.

Data on RR, toxicity, specifically grade 3 or higher peripheral neuropathy (PN) and deep vein thrombosis (DVT), PFS and OS were pooled under a random effects model.[11] If relevant summary statistics were not readily available for the time-to-event data from the published articles, the methods described by

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Parmar *et al*.[12] were used. Specifically, information on observed number of events and reported *P*-value from the log-rank-test statistic was used to derive the point estimate and the variance of the log hazard ratio. The overall summary hazard ratios (HR) or odds ratios (OR) along with the corresponding 95% confidence intervals (CI) under a random effects model are reported.

The consistency of effects across studies was assessed using the Cochran's Q based on a χ^2 statistic. However, given the small numbers of studies included in this meta-analysis, these statistics did not have sufficient power to detect true heterogeneity, and also did not adequately address whether the extent of heterogeneity impacts the final conclusions. Thus, heterogeneity was also assessed using I^2, where values of I^2 from 0% to 25% denote low heterogeneity, from 25.1–50% indicate moderate heterogeneity, and greater than 50% indicate high heterogeneity.[13] The Begg and Egger funnel plot was used to assess publication bias.[14,15] All statistical tests were two-sided, and the analyses were performed using the Comprehensive Meta Analysis Software Version 2.2 (Biostat, Englewood, NJ, USA).

Results

Description of trials

Overall, six prospective RCTs comparing MP with MPT regimen were identified.[6–10,16] Because of incomplete data reporting, we had excluded from our analysis, the Turkish trial (reported in abstract form) which had only commented upon the RRs and adverse events.[16] Data were extractable from the remaining five published RCTs for endpoints of ORR, OS and PFS.[6–10] Table 1 outlines in detail the features of the five trials comprising a total of 1568 patients included in the analysis. All five RCTs reported RRs and grade 3 and 4 DVT and PN. The primary end-points were either PFS, EFS or OS, with some variations in the definitions of these outcome measures across the trials.

Quality of the trials

All studies were RCTs with an adequate randomization procedure (Table 1). Two trials had placebo-controlled designs wherein the study drug was blinded from the investigators, the patients and the monitors thereby, protecting against the biases observed in open-labeled studies. All the included trials have now been published. The Begg and Egger funnel plot for OS demonstrated a symmetric distribution ($P=0.6$) indicating no significant publication bias. Per initial design all the trials were appropriately powered for the respective primary endpoint. However, none of the trials went to full accrual and were stopped early because of the recommendations of the data safety monitoring boards or based on external evidence or slow accrual.

Overall response rates, progression-free survival and overall survival

The pooled HR for OS and PFS were 0.80 ($P=0.07$; 95% CI: 0.63–1.02, Figure 1) and 0.68 ($P<0.001$, 95% CI: 0.55–0.82, Figure 2), respectively, in favor of MPT. The pooled OR of responding to treatment with MPT vs MP was 3.39 ($P<0.001$, 95% CI: 2.24–5.12, Figure 3) indicating that MP was significantly less effective than MPT in achieving at least a partial response.

Toxicity

Table 1 outlines the toxicities primarily observed. We analyzed two well-known thalidomide-related adverse effects of significant consequence in the patients assigned to the two treatments across the trials. Data were available for 1485 and 1377 patients for PN and DVT, respectively. The OR of grade 3 or higher PN and DVT were 6.61 ($P<0.001$) and 2.43 ($P=0.02$), respectively, (Figures 4a and b) in favor of MP.

Heterogeneity and sensitivity analysis

The test of heterogeneity among all RCTs was statistically significant in the estimate of RR ($\chi^2=13.63$; $P=0.009$ (df = 4); $I^2=70.1\%$), PFS ($\chi^2=11.08$; $P=0.03$ (df = 4); $I^2=63.9\%$), and OS ($\chi^2=12.55$; $P=0.01$ (df = 4); $I^2=68.1\%$).

Table 2 outlines the results of the sensitivity analysis for endpoints of OS and PFS. Significant heterogeneity persisted despite removal of GIMEMA or HOVON-49 studies. However, exclusion of the Nordic study from the analysis decreased the heterogeneity across studies ($I^2=42\%$ and 40.2% for OS and PFS, respectively; $P=$ NS). In addition, removal of studies using maintenance T (GIMEMA, HOVON-49 and Nordic) or vice versa (IFM trials) resulted in marked reduction in heterogeneity (Table 2).

Discussion

Melphalan has been the mainstay of therapy of MM patients for more than half a century. Prednisone as a single agent has also been shown to produce an objective response rate of 44% in a reanalysis of two myeloma treatment protocols.[17] The classic MP combination was born in 1969 when a trial of 183 patients with melphalan versus MP demonstrated a survival improvement by 6 months in MP arm.[18] Over the next 3 decades, multiple combination chemotherapies were compared with MP, yielding conflicting results. A meta-analysis of 18 trials suggested no difference in therapeutic efficacy.[19] The debate on greater efficacy of these aggressive combination regimens was eventually put to rest in 1998 when an individual pooled data overview of 4930 patients from twenty RCTs (with the addition of published data on another 1703 patients from seven trials) demonstrated no significant difference in OS with combination chemotherapies over MP despite significantly higher RRs (60 v 53.2%; $P<0.00001$).[20] Thus, the less toxic MP regimen remained the standard of care.

Myeloablative doses of melphalan with stem-cell rescue further improved median OS, and consequently became the most acceptable management strategy for transplant eligible patients.[5,21,22] In 1990s, a landmark trial demonstrated an objective response of 32% with thalidomide in relapsed and refractory MM.[23] In combination with dexamethasone (D), the RRs increased to 41–65%.[24–26] In the front-line setting, TD showed a higher RR (63 vs 41% for D, $P=0.001$) and time to progression at the cost of substantially higher grades 3 and 4 DVT (17 vs 3%) and PN (7 vs 4%).[27]

Typically, combination regimens can be justified when mechanisms for synergy are clearly defined. Despite highly potent *in vivo* effects, the preclinical activity of thalidomide in MM is modest, and synergy of thalidomide, which requires conversion to an active metabolite, with melphalan, is difficult to ascertain *in vitro*. Clinically, however, Offidani *et al*.[28] demonstrated greater activity of oral TM regimen over thalidomide alone (2-year PFS, 61 vs 45% with $P=0.037$) but OS difference was not noted.

In elderly patients and those who are transplant ineligible for reasons besides chronological age, the therapeutic approaches

Table 1 Trial characteristics

	GIMEMA	*IFM 99-06*	*IFM 01-01*	*NORDIC*	*HOVON 49*
Accrual period	01/2002–05/2005	05/2000–08/2005	04/2002–12/2006	01/2002–05/2007	09/2002–07/2007
Number of patients	331	321	226	357	333
MP	164	196	116	175	168
MPT	167	125	113	182	165
Median follow-up (months)	38.4	51.5	47.5	42	39
Inclusion criteria	>60 yrs or any age, but transplant ineligible	65–75 yrs or transplant ineligible if <65 yrs	⩾75 yrs	Any age, but ineligible for transplant	⩾65 yrs, PS ⩽3
Median Age (years)	72	69	78.5	74	72
Range	60–85	65–75	75–89	49–92	65–87
ECOG performance status 3–4 (%)	5	8	7	30	0.04
Total number of cycles planned	6	12 cycles q6 weeks	12 cycles q6 weeks	Until plateau	8 cycles q4 weeks, if ongoing response then until plateau
Doses					
M	4 mg/m^2 × 7 days	0.25 mg/kg × 4 days	0.2 mg/kg per day × 4 days	0.25 mg/kg × 4 days	0.25 mg/kg × 5 days
P	40 mg/m^2 × 7 days	2 mg/kg × 4 days	2 mg/kg per da y × 4 days	100 mg per day × 4 days	1 mg/kg × 5 days
T	100 mg per day	Dose of T not standardized, 400 mg per day maximum dose	100 mg per day	200 mg per day × 7 days then 400 mg per day	200 mg per day
T maintenance in MPT arm	Yes, 100 mg per day until relapse/ refractory disease	No	No	Yes, 200 mg per day	Yes, 50 mg per day
Primary End Point	RR/PFS	OS	OS	OS	EFS
Secondary End Point	OS Prognostic factors Toxicity frequency	PFS RR	PFS RR safety	PFS RR TTP QOL	OS RR PFS QOL
A priori sample-size calculations performed;	Yes	Yes	Yes	Yes	Yes
Original number of planned patients	380	500	280	800	420
Accrual	Recruitment stopped at 331 patients as clear ORR advantage of MPT noted on interim analysis	Recruitment stopped at 447 patients as clear OS advantage of MPT noted on unplanned interim analysis	Recruitment stopped at 232 patients because of survival advantage of MPT in IFM 99-06 trial and because MPT was officially made available to HDT ineligible NDMM patients	Accrual stopped at 357 patients; effective power reduced from 80 to 72% to detect HR of 1.4	Accrual stopped at 344 patients based on other publication reports indicating superior effect
Study design	Open labeled; ITT	Open labeled; ITT	Placebo-controlled design, ITT	Placebo-controlled design, ITT	Open labeled; ITT
ORR (%)					
MP	85	35	31	66 (including MR)	45
MPT	51	76	62	71 (including MR)	66
CR					
MP	4	2	1	4	NR
MPT	16	13	7	13	NR
CR+VGPR					
MP	15	7	7	7	8
MPT	45	47	21	23	28
PFS (months)					
MP	14.5	17.8	18.5	14	21
MPT	21.8	27.5	24.1	15	33
OS (months)					
MP	47.6	33.2	29	32	31
MPT	45	51.6	44	29	40

Table 1 (*Continued*)

	GIMEMA	*IFM 99-06*	*IFM 01-01*	*NORDIC*	*HOVON 49*
Grade 3–4 Toxicity[a] *(%)*					
PN					
MP	0	0	2	1	4
MPT	10	6	2	6	23
Venous Thromboembolism					
MP	2	4	3	8	0
MPT	11	12	6	8	3
Neutropenia					
MP	17	26	9	20	NR
MPT	16	48	23	25	NR
Infection					
MP	2	9	NR	10	18
MPT	10	13	NR	15	28
Constipation					
MP	0	0	10 (⩾Grade 2)	6	NR
MPT	6	10	17 (⩾Grade 2)	3	NR
DVT Prophylaxis	Not initially, but started in Dec 2003; LMWH with first 4 cycles	No routine prophylaxis recommended	No routine prophylaxis recommended	No routine prophylaxis recommended	Not initially; Jan 2005 LMWH with MPT and ASA with T maintenance
Response criteria	EBMT/IBMTR	Own definitions, VGPR also included	Own definitions, VGPR also included	Own definitions, MR and VGPR also included	Own definitions, VGPR also included
Median duration of T therapy (months)	9.6	11	13.5	7.7 for those living longer than 1 year	8.4 months as maintenance
Total dose of M if completed assigned schedule at recommended maximum dose	4 mg/kg	12 mg/kg	9.6 mg/kg	Incalculable[b]	Incalculable[b]

Abbreviations: ASA, aspirin; CR, complete response; DVT, deep vein thrombosis; EFS, event-free survival; EBMT/IBMTR, European bone marrow transplantation/international bone marrow transplantation registry; ECOG, Eastern cooperative oncology group; GIMEMA, Gruppo Italiano Mallattie Ematologiche dell'Adulto; HDT, high dose therapy; HOVON, Hemato-Oncologie voor Volwassennen Nederland; IFM, Intergroupe Francophone du Myélome; ITT, intention to treat; LMWH, low molecular weight heparin; MR, minor response; M, melphalan; MPT, melphalan, prednisone and thalidomide; NDMM, newly diagnosed multiple myeloma; NR, not reported; ORR, overall response rates; OS, overall survival; P, prednisone; PN, peripheral neuropathy; PFS, progression-free survival; PR, partial response; QOL, quality of life; RR, response rate; TTP, time to progression; T, thalidomide; VGPR, very good partial response; Yrs, Years.
[a]National Cancer Institute Common Toxicity Criteria.
[b]As melphalan was given until plateau.

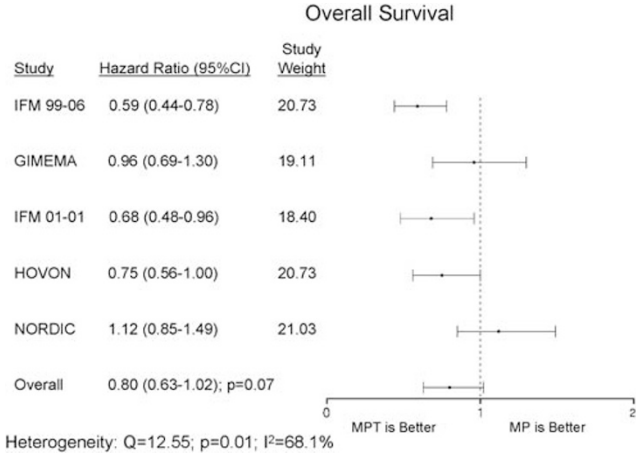

Figure 1 Forest plot of individual and overall summary effect estimate (HR) along with 95% CI for OS.

are inadequate. Renal failure, hepatic dysfunction, pulmonary and cardiac issues that render a patient ineligible for transplant may reduce the efficacy of standard regimens. Furthermore, poor performance status has adverse implications on outcomes. Elderly patients are particularly susceptible to drug-related side effects, and use of ultra low doses of thalidomide (25 mg/day) has been shown to improve outcome of patients with poor functional status.[29]

In 2002, a single UK Myeloma Forum Study involving 22 transplants ineligible patients (13 untreated, 9 previously treated) attempted to assess the safety and efficacy of MPT in patients. Although a 41% PR rate was noted, the study was closed prematurely because of the high incidence (3/13) of venous thromboembolism.[30]

In the newly diagnosed MM patients, six phase III trials comparing MPT with MP have been conducted to date following promising results of a phase II study by Palumbo *et al*.[31,32] However, somewhat conflicting conclusions of these trials has made the interpretation difficult. Although disparate outcomes could be attributed to different study designs and patient populations in these trials, our meta-analysis attempted to answer the critically pertinent question of benefit, or lack thereof, of adding thalidomide to the conventional MP regimen.

Interestingly, all trials were conducted in the European Union where patients of 65 years or older are generally not offered ASCT. The quest for effective therapeutic approaches in this cohort of patients is important because the median age of MM patients at diagnosis is ~70 years.

A closer look at the studies included in our analysis identifies distinctive features of each one that could possibly have

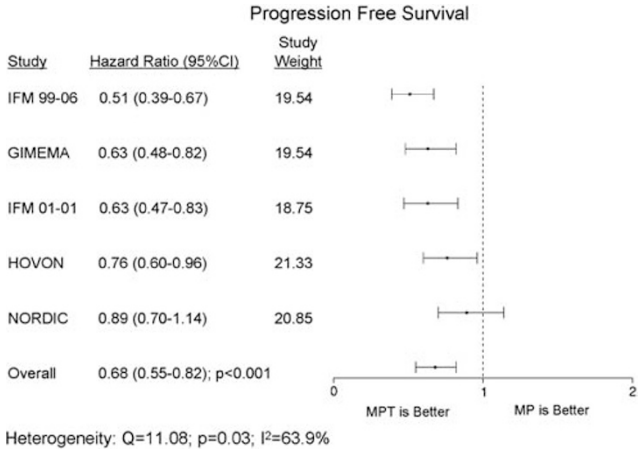

Figure 2 Forest plot of individual and overall summary effect estimate (HR) along with 95% CI for PFS.

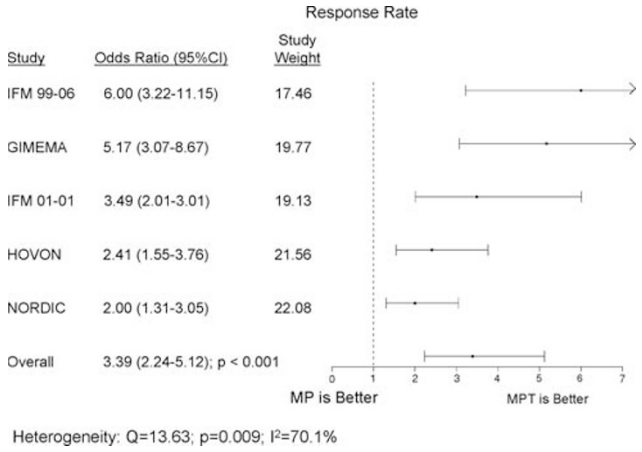

Figure 3 Forest plot of individual and overall summary effect estimate (OR) along with 95% CI for RRs.

influenced outcomes (Table 1). As systematic reviews analyze studies that are diverse both clinically and methodologically, heterogeneity in the outcomes is not unexpected. In our meta-analysis heterogeneity has likely arisen as a consequence of differences in the definitions of outcome measures, duration of follow-up, drug dosages and inclusion criteria. In addition, maintenance therapy was used in only three out of the five studies. Although in the GIMEMA trial, PFS and OS were calculated from the time of diagnosis, these end-points were calculated from the time of random assignment or registration for the others.[8] Outcomes based on adequate genetic risk stratification, which has substantial prognostic implications, were mostly unavailable in these trials. While the HOVON-49 and IFM-01-01 studies focused exclusively on patients greater than 65 years and 75 years of age, respectively, IFM 99-06 enrolled patients between 65–75 years or less than 65 years, if transplant ineligible.[6,7,10] The other two trials permitted enrollment of any transplant ineligible patient irrespective of age.[8,9] The exclusive enrollment of patients above 75 years of age in IFM 01-01 trial is noteworthy as it focused on the often excluded, but sizable proportion (~20%) of myeloma patients.[7] The Nordic study cohort was remarkable for involvement of 30% patients with poor performance status (ECOG 3 and 4), a sub-group that is mostly inadequately represented in clinical trials performed currently.[9]

Importantly, the dose intensities of all three drugs (M, P and T) differed amongst the five trials. Melphalan and thalidomide doses were lowest in IFM 01-01 study (involving patients above 75 years of age), yet it demonstrated survival advantage of MPT arm.[7] Although evaluation of optimal dose of thalidomide was not the objective of any of the trials, the Nordic group made an important indirect inference from their study that better tolerated lower doses of thalidomide (100–200 mg) were sufficient and comparable to higher doses of thalidomide at 400 mg used in their induction phase and 200 mg in the maintenance phase.[9] With such high doses, better RRs did not translate into survival benefit in the MPT arm.[9] Moreover, nearly a third of patients had discontinued treatment by 3 months, and cessation of therapy increased to 56% by end of first year. Furthermore, during the first 6 months of treatment, the Nordic study reported 35 deaths in the MPT arm, 23 among patients older than 75 years of age.[9] Importantly, the three non-French trial designs[8–10] included maintenance therapy with thalidomide in the MPT arm, further complicating cross-trial comparisons with the two IFM studies.[6,7] The IFM 99-06 also included a third arm of VAD induction followed by melphalan at 100 mg/m^2 with stem-cell rescue.

RRs of VGPR or greater in MPT arms were comparable (47 vs 45%) between IFM 96-06 and the Italian study, with similar PFS (27.5 months vs 21.8 months).[6,8] Yet the longer PFS of MPT arm in the Italian study did not result in substantially improved OS. On relapse or progression, 41% of patients in the MP arm in this study crossed over to receive bortezomib or thalidomide-based regimes, which probably accounts for lack of survival advantage with upfront MPT.[8] Similarly, in the Nordic study OS was comparable between the two arms, despite protracted maintenance therapy with high doses (200 mg/day) of thalidomide, and attainment of longer PFS in patients receiving MPT.[9]

A sensitivity analysis was performed to detect studies leading to significant heterogeneity in our analysis. The two French trials with straightforward designs of random assignments to MP or MPT, without thalidomide maintenance, demonstrated superior outcome in all survival endpoints in the MPT arm. Exclusion of studies with T maintenance therapy resulted in complete disappearance of heterogeneity for OS. When the Nordic study was excluded from the analysis, the heterogeneity across trials became insignificant for both PFS and OS outcomes (Table 2).

Concurrent administration of myelosuppressive drugs has the potential to enhance the adverse effects and requires dose reduction as compared with monotherapy. Although a higher incidence of grade 3 or 4 neutropenia was observed in the MPT arms of both the IFM studies, no differences in severe infections were noted compared to MP. In contrast, the GIMEMA study demonstrated more frequent severe infections in the MPT arm despite lack of any observable difference in the rates of neutropenia between the two groups.

Venous thromboembolism is a known adverse effect of thalidomide. None of the trials used deep venous thrombosis (DVT) prophylaxis initially. Only GIMEMA and HOVON-49 study protocols were subsequently revised to include prophylaxis against this complication.[8,10] The rates of thromboembolism were reduced from 20 to 3% with adequate DVT prophylaxis in GIMEMA study.[8] Although routine prophylaxis was not recommended in the Nordic study, the low incidence of DVT in the two arms may be explained by the use of drugs with anti-thrombotic effect in up to 40% of patients.[9] We now know that the risk of venous thromboembolism can be reduced by adhering to the current recommendations for the prevention of IMiD-induced DVT.[33]

The incidence of PN increases with prolonged use of thalidomide due to cumulative neurotoxicity. More than 50% of patients treated for a year suffered from PN, although in most

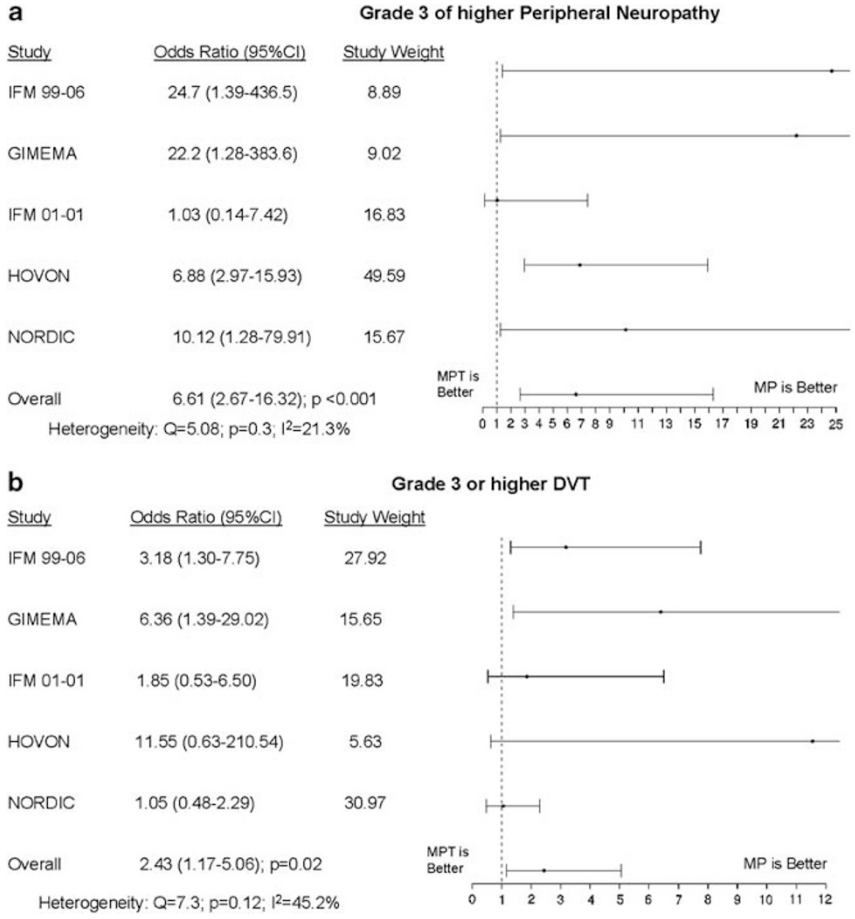

Figure 4 (**a**) Forest Plot of individual and overall summary effect estimate (OR) along with 95% CI for grade 3 or higher PN. (**b**) Forest Plot of individual and overall summary effect estimate (OR) along with 95% CI for grade 3 or higher deep vein thrombosis.

Table 2 Sensitivity analyses

Studies removed	I^2		*Significant heterogeneity at* P = *0.05*	
	OS (%)	*PFS* (%)	*OS*	*PFS*
GIMEMA	73	71.7	Yes	Yes
HOVON	75.6	70.1	Yes	Yes
NORDIC	42	40.2	No	No
GIMEMA and NORDIC	0	60.1	No	Borderline
GIMEMA, HOVON and NORDIC	0	11.8	No	No
IFM 01-01 and IFM 99-06	50.2	46	No	No
IFM99-06 and NORDIC	10.5	0	No	No

Abbreviations: GIMEMA, Gruppo Italiano Mallattie Ematologiche dell'adulto; HOVON, Hemato-Oncologie voor Volwassennen Nederland; IFM, Intergroupe Francophone du Myélome; OS, overall survival; PFS, progression-free survival.

patients enrolled in these studies it was of low grade ($\leqslant 2$). Treatments of shorter duration at lowest effective doses could decrease its incidence. In addition, physicians and patients should remain alerted, and promptly reduce/discontinue thalidomide upon development of painful paresthesias, onset of motor dysfunction, or interference with daily activities. Appropriate and timely prophylactic and therapeutic interventions can make these adverse effects manageable.

This meta-analysis successfully distills the discordant results of incorporated trials, taking into account the heterogeneity across the studies. Undoubtedly, despite substantial heterogeneity across studies, the overall RRs were overwhelmingly superior with addition of thalidomide (with or without maintenance) to MP, translating into significantly longer overall PFS and nearly significant OS benefit in our analysis. The grades 3 and 4 toxicities of DVT and PN, as expected, were substantially higher with the three-drug regimen.

Over the last few years, regimens incorporating the combination of MP with novel agents have improved the treatment of transplant ineligible patients. The ORR and PFS with MPT-based trials are comparable to those seen in the VISTA trial involving VMP (ORR = 71%, PFS = ~24 months), an effective, alternative

Table 3 Proposed MPT regimen for transplant ineligible and/or elderly myeloma patients

Age	*Regimen*	*Duration*
<75 years	Melphalan: 0.25 mg/kg per day for 4 days Prednisone: 2 mg/kg per day for 4 days Thalidomide: 100–200 mg per day continuously as tolerated	Every 6 weeks for 12 cycles (total 18 months)
⩾75 years	Melphalan: 0.20 mg/kg per day for 4 days Prednisone: 2 mg/kg per day for 4 days Thalidomide: 50–100 mg per day[a] continuously	Every 6 weeks for 12 cycles (total 18 months)

[a]Dose of thalidomide should be promptly reduced by 50% with Grade 1 to Grade II peripheral neuropathy or intolerance. In the absence of data, for patients ⩾75 years of age some experts suggest using melphalan at 0.13–0.18 mg/kg and thalidomide at 50 mg daily or every other day.

regimen for the elderly, transplant ineligible patients.[34] MPR is another effective regimen, and an ongoing ECOG trial is comparing MPR with MPT regimen.[35] Recently, a three-drug regimen, ThaDD (thalidomide, pegylated liposomal doxorubicin and intermediate dose dexamethasone) has demonstrated significantly higher overall response (87.5 vs 61.5%) compared with MPT in patients over 75 years, without any significant improvement in PFS and OS.[36] Another phase III, multicenter, randomized trial comparing efficacy and safety of lenalidomide plus low-dose dexamethasone (Rd) with MPT is currently underway (http://www.cancer.gov/search/ResultsClinicalTrials.aspx?protocolsearchid=7963791).

Reassuringly, the results of our meta-analysis seem to be similar to the recently presented abstract of individual pooled data analysis of six RCTs (PFS, HR = 0.67 (CI: 0.55–0.80); OS, HR = 0.82, (CI: 0.66–1.02)), which included the patients enrolled by the Turkish Myeloma Study Group.[37] This individual patient data analysis of 1682 subjects confirmed a significant impact on PFS and a nearly significant difference in the OS with addition of T to MP.[37] Our robust outcome data allow us to state with reasonable confidence that this three-drug regimen seems to have superior outcome, albeit at a cost of greater toxicity. Although it is our overriding recommendation that whenever feasible, elderly patients be enrolled in clinical trials, outside of a clinical trial setting, if MPT is considered, the doses have to be carefully adjusted. In particular, increasing the dose of thalidomide in the very elderly population can be associated with adverse outcomes as demonstrated by the Nordic trial. As such, one proposal in the absence of well-defined, optimal dosage of thalidomide, and more in line with the IFM 99-06 and IFM 01-01 regimens, is outlined in Table 3. In conclusion, MPT can be considered one of the new standards of care for elderly and/or transplant ineligible MM patients. Randomized trials comparing other new combination regimens with MPT would further advance the field for such patients who comprise a sizable proportion of the myeloma patient-population.

Conflict of interest

Shaji Kumar receives research support for clinical trials from Celgene, Novartis, Millennium, Bayer, Genzyme, Merck and Cephalon. Angela Dispenzieri and Martha Q Lacy receive research funding from Celgene. Philip R Greipp receives research-funding grants from Celgene and Novartis, and is on the advisory board of Amgen. Morie A Gertz receives research support from Millennium and Novartis, and honorarium from Celgene and Millennium. Robert A Kyle has been on the disease and/or data monitoring committees of Celgene, Novartis, Merck, Bristol-Myers Squibb Keryx Biopharmaceuticals, Onyx Pharmaceuticals and Johnson and Johnson sponsored studies. He is also a consultant for Millennium and receives honoraria from Binding Site. The remaining authors have no conflicts of interest to declare.

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Author Contributions

SVR and SK conceived the study; PK, SVR, SK and SJM collected the data; PK, SJM and SK wrote the manuscript; SJM performed statistical analysis; SJM, PK, SK, MQL, AD, MAG, JRM, DD, VR, RAK, PRG and SVR interpreted the data; SVR, DD, AD, MQ L, JRM, MAG, PRG and RAK edited the manuscript.

References

1 Kyle RA, Rajkumar SV. Multiple myeloma. *N Engl J Med* 2004; **351**: 1860–1873.
2 Badros A, Barlogie B, Siegel E, Morris C, Desikan R, Zangari M *et al.* Autologous stem cell transplantation in elderly multiple myeloma patients over the age of 70 years. *Br J Haematol* 2001; **114**: 600–607.
3 Kumar SK, Hayman SR, Kyle RA. Autologous stem cell transplantation in the elderly including pre- and post-treatment options. *Bone Marrow Transplantation* 2007; **40**: 1115–1121.
4 Reece DE, Bredeson C, Perez WS, Jagannath S, Zhang MJ, Ballen KK *et al.* Autologous stem cell transplantation in multiple myeloma patients <60 vs >/=60 years of age. *Bone marrow transplantation* 2003; **32**: 1135–1143.
5 Harousseau JL, Moreau P. Autologous hematopoietic stem-cell transplantation for multiple myeloma. *N Engl J Med* 2009; **360**: 2645–2654.
6 Facon T, Mary JY, Hulin C, Benboubker L, Attal M, Pegourie B *et al.* Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial. *Lancet* 2007; **370**: 1209–1218.
7 Hulin C, Facon T, Rodon P, Pegourie B, Benboubker L, Doyen C *et al.* Efficacy of melphalan and prednisone plus thalidomide in patients older than 75 years with newly diagnosed multiple myeloma: IFM 01/01 trial. *J Clin Oncol* 2009; **27**: 3664–3670.
8 Palumbo A, Bringhen S, Liberati AM, Caravita T, Falcone A, Callea V *et al.* Oral melphalan, prednisone, and thalidomide in elderly patients with multiple myeloma: updated results of a randomized controlled trial. *Blood* 2008; **112**: 3107–3114.
9 Waage A, Gimsing P, Fayers P, Abildgaard N, Ahlberg L, Bjorkstrand B *et al.* Melphalan and prednisone plus thalidomide or placebo in elderly patients with multiple myeloma. *Blood* 2010; **116**: 1405–1412.
10 Wijermans P, Schaafsma M, Termorshuizen F, Ammerlaan R, Wittebol S, Sinnige H *et al.* Phase III study of the value of

thalidomide added to melphalan plus prednisone in elderly patients with newly diagnosed multiple myeloma: the HOVON 49 Study. *J Clin Oncol* 2010; **28**: 3160–3166.
11 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**: 177–188.
12 Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Stat Med* 1998; **17**: 2815–2834.
13 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ (Clinical research ed)* 2003; **327**: 557–560.
14 Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994; **50**: 1088–1101.
15 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ (Clinical research ed)* 1997; **315**: 629–634.
16 Beksac M, Haznedar R, Firatli-Tuglular T, Ozdogu H, Aydogdu I, Konuk N, Sucak G *et al*. Addition of thalidomide (t) to oral melphalan/prednisone (mp) in patients with multiple myeloma: initial results of a randomized trial from the turkish myeloma study group. *Blood* 2010, Blood (ASH Annual Meeting Abstracts) **114**: 1880.
17 McIntyre OR, Pajak TF, Kyle RA, Cornwell III GG, Leone L. Response rate and survival in myeloma patients receiving prednisone alone. *Med Pediatr Oncol* 1985; **13**: 239–243.
18 Alexanian R, Haut A, Khan AU, Lane M, McKelvey EM, Migliore PJ *et al*. Treatment for multiple myeloma. Combination chemotherapy with different melphalan dose regimens. *Jama* 1969; **208**: 1680–1685.
19 Gregory WM, Richards MA, Malpas JS. Combination chemotherapy versus melphalan and prednisolone in the treatment of multiple myeloma: an overview of published trials. *J Clin Oncol* 1992; **10**: 334–342.
20 Combination chemotherapy versus melphalan plus prednisone as treatment for multiple myeloma: an overview of 6,633 patients from 27 randomized trials. Myeloma Trialists' Collaborative Group. *J Clin Oncol* 1998; **16**: 3832–3842.
21 Attal M, Harousseau JL, Leyvraz S, Doyen C, Hulin C, Benboubker L *et al*. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. *Blood* 2006; **108**: 3289–3294.
22 Child JA, Morgan GJ, Davies FE, Owen RG, Bell SE, Hawkins K *et al*. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. *N Engl J Med* 2003; **348**: 1875–1883.
23 Singhal S, Mehta J, Desikan R, Ayers D, Roberson P, Eddlemon P *et al*. Antitumor activity of thalidomide in refractory multiple myeloma. *N Engl J Med* 1999; **341**: 1565–1571.
24 Dimopoulos MA, Zervas K, Kouvatseas G, Galani E, Grigoraki V, Kiamouris C *et al*. Thalidomide and dexamethasone combination for refractory multiple myeloma. *Ann Oncol* 2001; **12**: 991–995.
25 Palumbo A, Bertola A, Falco P, Rosato R, Cavallo F, Giaccone L *et al*. Efficacy of low-dose thalidomide and dexamethasone as first salvage regimen in multiple myeloma. *Hematol J* 2004; **5**: 318–324.
26 Palumbo A, Giaccone L, Bertola A, Pregno P, Bringhen S, Rus C *et al*. Low-dose thalidomide plus dexamethasone is an effective salvage therapy for advanced myeloma. *Haematologica* 2001; **86**: 399–403.
27 Rajkumar SV, Blood E, Vesole D, Fonseca R, Greipp PR. Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. *J Clin Oncol* 2006; **24**: 431–436.
28 Offidani M, Marconi M, Corvatta L, Olivieri A, Catarini M, Leoni P. Thalidomide plus oral melphalan for advanced multiple myeloma: a phase II study. *Haematologica* 2003; **88**: 1432–1433.
29 Patrick HE, Bowcock SJ. Ultra low dose thalidomide in myeloma revisited. *Br j Haematol* 2010; **150**: 232–234.
30 Oakervee HBH, Boots M, Olujohungbe A, Smith S, Williams C. A study of safety and efficacy of oral melphalan,prednisone and thalidomide (MPT) in the treatment of multiple myeloma: a UK Myeloma Forum Pilot Study (abstract). *Br J Haematol* 2002; **117** (Suppl 1): 66.
31 Palumbo A, Bertola A, Musto P, Caravita T, Callea V, Nunzi M *et al*. Oral melphalan, prednisone, and thalidomide for newly diagnosed patients with myeloma. *Cancer* 2005; **104**: 1428–1433.
32 Palumbo A, Bringhen S, Caravita T, Merla E, Capparella V, Callea V *et al*. Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. *Lancet* 2006; **367**: 825–831.
33 Palumbo A, Rajkumar SV, Dimopoulos MA, Richardson PG, San Miguel J, Barlogie B *et al*. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. *Leukemia* 2008; **22**: 414–423.
34 San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M *et al*. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. *N Engl J Med* 2008; **359**: 906–917.
35 Palumbo A, Falco P, Corradini P, Falcone A, Di Raimondo F, Giuliani N *et al*. Melphalan, prednisone, and lenalidomide treatment for newly diagnosed myeloma: a report from the GIMEMA–Italian Multiple Myeloma Network. *J Clin Oncol* 2007; **25**: 4459–4465.
36 Offidani M, Leoni P, Bringhen S, Corvatta L, Larocca A, Gentili S *et al*. Melphalan, prednisone, and thalidomide versus thalidomide, dexamethasone, and pegylated liposomal doxorubicin regimen in very elderly patients with multiple myeloma: a case-match study. *Leuk lymphoma* 2010; **51**: 1444–1449.
37 Waage APP, Fayers P, Beksac M, Hulin C, Mary J, Bringhen S *et al*. MP versus MPT for previously untreated elderly patients with multiple myeloma: A meta-analysis of 1,682 individual patient data from six randomized clinical trials. *J Clin Oncol* 2010; **28**: 2010 (suppl; abstr 8130).