Thalidomide-based Regimens for Elderly and/or Transplant Ineligible Patients with Multiple Myeloma: A Meta-analysis

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Abstract

Background: Thalidomide is an immunomodulatory and anti-angiogenic drug that has shown promise in patients with myeloma. Trials comparing efficacy of standard melphalan and prednisone (MP) therapy with MP plus thalidomide (MPT) in transplant-ineligible or elderly patients with multiple myeloma (MM) have provided conflicting evidence. This meta-analysis aimed to determine the efficacy and toxicity of thalidomide in previously untreated elderly patients with myeloma.

Methods: Medline, the Cochrane Controlled Trials register, conference proceedings of the American Society of Hematology (1995–2014), the American Society of Clinical Oncology (1995–2014), and CBM, VIP, and CNKI databases were searched for randomized control trials with the use of the medical subject headings "MM" and "thalidomide". Trials were assessed by two reviewers for eligibility. Meta-analysis was conducted using a fixed effects model. Sensitivity analysis was performed to test the robustness of the findings.

Results: Overall, seven trials were identified, covering a total of 1821 subjects. The summary hazard ratio (thalidomide vs. control) was 0.82 (95% confidence interval [CI]: 0.72–0.94) for overall survival (OS), and 0.65 (95% CI: 0.58–0.73) for progression-free survival, in favor of thalidomide treated group. The risk ratio of complete response with induction thalidomide was 3.48 (95% CI: 2.24–5.41). A higher rate of III/IV adverse events were observed in MPT arm compared with the MP arm. However, analysis of sub-groups administering anticoagulation as venous thromboembolism prophylaxis suggested no difference in relative risk of thrombotic events between two arms ($RR = 1.47$, 95% CI: 0.43–5.07, $P = 0.54$). Further analysis of trials on the treatment effects of MPT versus MP on adverse events-related mortality showed no statistical difference between two arms ($RR = 1.24$, 95% CI: [0.95–1.63], $P = 0.120$).

Conclusion: Thalidomide appears to improve the OS of elderly and/or transplant-ineligible patients with MM when it is added to standard MP therapy.

Key words: Elderly; Meta-analysis; Multiple Myeloma; Thalidomide

Introduction

Multiple myeloma (MM) is one of the hematologic malignancies with a poor prognosis, characterized by a neoplastic proliferation of monoclonal plasma cells.[1] There has been considerable progress in the treatment of MM in recent years. High-dose melphalan with autologous stem-cell transplantation improves overall survival (OS) in patients with MM, who are <65 years old.[2,3] However, because myeloma is predominantly a disease of older patients, transplantation is an option for only approximately 50% of the patients with myeloma.

The introduction of novel agents over the last decade has transformed the therapy for MM, especially for transplant-ineligible MM patients. Thalidomide is an oral, immunomodulatory, and anti-angiogenesis drug that has shown promise in patients with myeloma. Some early trials suggested that thalidomide has activity as initial treatment for older patients with myeloma.[4] However, the awareness of risks of thalidomide is also increasing, especially a substantial risk of venous thromboembolism (VTE).[4,5] Trials comparing efficacy of standard melphalan and prednisone

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(MP) therapy with MP plus thalidomide (MPT) in transplant-ineligible or elderly patients with MM have provided conflicting evidence. There were also no consistent results about the OS in reported meta-analysis.[6-8] With results variable, we did this update meta-analysis to define whether thalidomide exposure upfront would have an adverse impact on OS and progression-free survival (PFS) or not and integrate the existing outcome data related to the efficacy of MP versus MPT.

METHODS

Literature search strategy
Pubmed, the Cochrane Library and conference proceedings of the American Society of Hematology (ASH) (1995–2014), the American Society of Clinical Oncology (ASCO) (1995–2014), and CBM, VIP, and CNKI databases were searched for randomized control trials (RCTs) with the use of the medical subject headings "MM" and "thalidomide." Reference lists from studies selected for this review were also hand searched.

Study selection
Studies were eligible for inclusion in the meta-analysis if they met all the following criteria: (1) they were published up to December 2014 and written in English or Chinese, (2) they dealt only with untreated myeloma patients, and (3) they provided data on PFS and/or OS. Multiple reports of a single study were considered one publication, and only the most recent or complete article was examined. All potentially relevant articles were reviewed by two independent investigators (Wen-Wen Lyu and De-Hai Song). Disagreements were resolved by a third author (Jin-Jie Zhang).

Outcome measures
The primary outcome of this review was OS. Secondary outcomes were PFS, response rates, and grade III/IV adverse events (especially about the peripheral neuropathy, thrombotic events, and infections). PFS was measured from the date of enrolment, randomization, or start of treatment until disease progression, relapse, or death. OS was measured from the date of enrolment, randomization, or start of treatment until death from any cause. Time to event outcomes are most appropriately analyzed using hazard ratios (*HR*s). In the absence of individual patient data, *HR*s and/or associated statistics were available from the reported methods.[9]

Data extraction and quality assessment
Two reviewers (Wen-Wen Lyu and De-Hai Song) independently and blindly screened the titles and abstracts of all identified studies and then assessed eligibility for inclusion, assessed studies' methodological quality.[10]

Statistical analysis
Time to event data (OS, PFS) were pooled and reported as *HR* while dichotomous data (complete response rate and adverse event rates) were expressed as *RR*, respectively, using a 95% confidence interval (*CI*). Forest plots of *HR*s

were completed using the inverse variance method. The consistency of effects across studies was assessed using the Cochran's Q based on a λ^2 statistic. A *P* value of <0.05 was defined as statistically significant for all outcomes. Heterogeneity was also assessed using I^2, where values of I^2 from 0% to 25% denote low heterogeneity, from 25% to 50% indicate moderate heterogeneity, and >50% indicate high heterogeneity.[11] Significant heterogeneity was explored with sub-group analysis. All meta-analyses were completed with the use of RevMan version 5.2 (The Nordic Cochrane Centre, Rigshospitalet, Denmark).

RESULTS

Characteristics of included trials
As illustrated in Figure 1, the initial literature search yielded 405 citations in English. After screening by one reviewer (Wen-Wen Lyu), 21 citations were identified as "possibly eligible" for inclusion. The abstracts and/or texts of all 21 citations were independently reviewed by two authors (Wen-Wen Lyu and De-Hai Song), yielding 7 published RCTs reported in English. ASH and ASCO abstracts were searched for unpublished RCTs, but no more additional RCTs were identified. Five clinical trials in Chinese finally searched were removed because of the lower quality (≤2 points, data not shown).

Seven trials in English enrolled a total of 1821 patients. Their characteristics are described in Table 1. All included seven RCTs[11-17] reported final analyses and intention to treat analyses.

Quality assessment
All the included trials have been published. All seven studies in English were RCTs with an adequate randomization procedure (jaded scores ≥3). All these studies reported intention to treat analyses.

Results of the meta-analysis
Efficacy assessments
The pooled risk ratio for complete response (CR) was 3.48 [*P* < 0.00001; 95% *CI*: 2.24–5.41; Figure 2] among all RCTs under the fix effects model. The CR was significantly
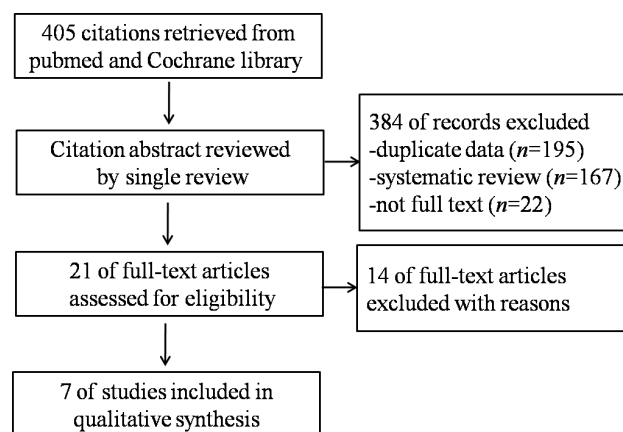

Figure 1: Study selection result.

improved by thalidomide-containing regimens. There was no statistically significant heterogeneity [$P = 0.23$; $I^2 = 27\%$; Figure 2] among pooled RCT studies for the outcome of CR.

Progression-free survival and overall survival

Pooled results showed a statistically significant difference with MPT use versus MP for OS. The combined HR for OS was 0.82 (95% CI: [0.72–0.94]; $P = 0.004$) [Figure 3]. There was also a statistically significant difference for the outcome of PFS (HR = 0.65; 95% CI: [0.58–0.73]; $P < 0.00001$) [Figure 4]. However, there was a high heterogeneity among included trials for the outcomes of OS ($I^2 = 53\%$, $P = 0.05$) and PFS ($I^2 = 54\%$, $P = 0.05$).

Sensitivity analysis

To assess the robustness of the effect of thalidomide addition to the MP regimen and to explain the heterogeneity observed for the outcome of OS and PFS, additional sensitivity analyses were performed. Table 2 outlines the results of the sensitivity analysis for endpoints of OS and PFS. Excluded every one of the other studies, the corresponding HR and 95% CI was similar beyond these two studies.[12,16] Heterogeneity between studies was decreased significantly after removal of these two studies.

Adverse events

Table 3 reports the safety profile. Grade 3 or 4 adverse events were observed more frequently in MPT group (RR = 2.30; 95% CI: 1.97–2.70; $P < 0.00001$). The incidence of neuropathy, thrombotic-embolism events, infection, and rash was higher in MPT treated patients. It was 9.1%, 8.1%, 13.9%, and 2.4% compared with 1.3%, 3.5%, 7.2%, and 0.28% in MP group, respectively.

Table 1: The characteristics of included randomized control trial

Author, year	N/n	Age, years		Therapy		Doses		
		MPT	MP	MPT	MP	M	P	T (mg/d)
Facon et al., 2007[12]	321/125	65–75		MPT × 12 cycles	MP × 12 cycles	0.25 mg/kg	2 mg/kg	≤400
Hulin et al., 2009[13]	229/113	75–89		MPT × 12 cycles	MP × 12 cycles	0.20 mg/kg	2 mg/kg	100
Palumbo et al., 2008[11]	331/167	72	72	MPT × 6 cycles, then T	MP × 6 cycles	10 mg/m²	40 mg/m²	100
Wijermans et al., 2010[15]	333/165	72	73	MPT × 8 cycles, then T	MP × 8 cycles	0.25 mg/kg	1 mg/kg	200
Waage et al., 2010[16]	357/182	74.6	74.1	MPT until plateau, then T	MP until plateau	0.25 mg/kg	100 mg/d	200–400
Beksac et al., 2010[14]	115/58	69	72	MPT × 8 cycles, then T	MP × 8 cycles	9 mg/m²	60 mg/m²	100
Sacchi et al., 2011[17]	135/70	76	79	MPT × 6–12 cycles, then T	MP ≥6 cycles, then dexa	0.25 mg/kg	60 mg/m²	100

MPT: Melphalan, prednisone, and thalidomide; MP: Melphalan and prednisone. T: Thalidomide; M: Melphalan; P: Prednisone; Dexa: Dexamethasone.
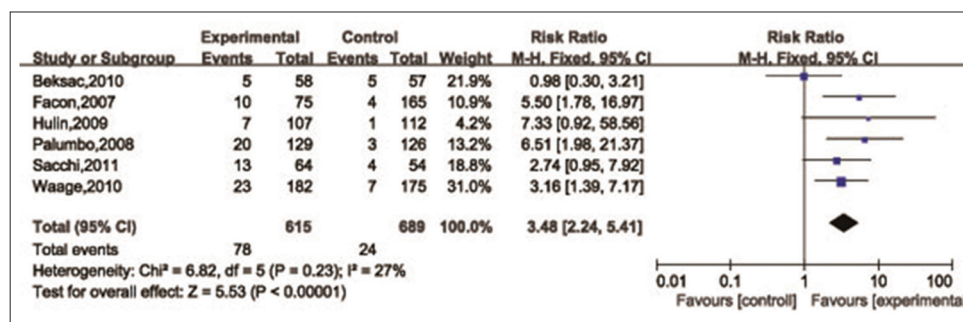

Figure 2: Statistics and corresponding forest plot for the risk ratio of complete response rate. The comparison is between melphalan, prednisone, and thalidomide versus control. RRs were calculated using a fixed-effects model.
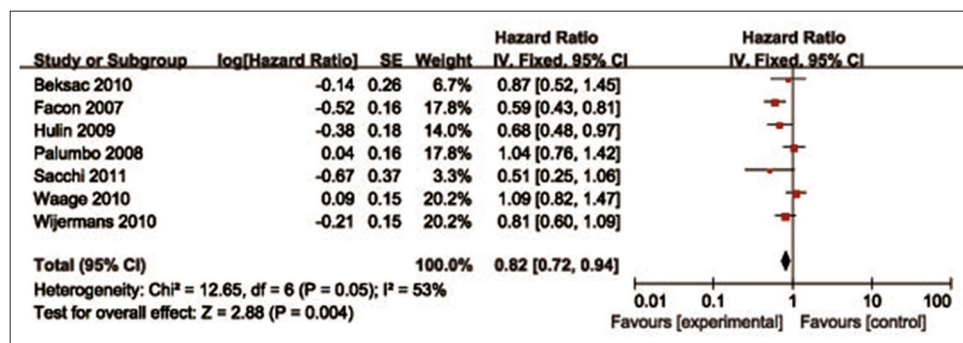

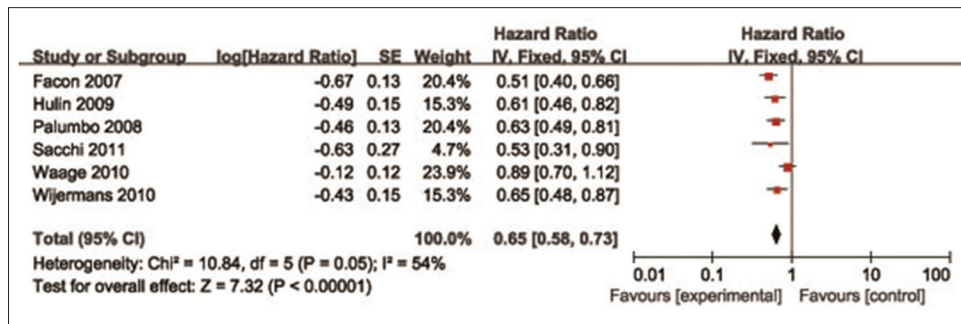**Figure 3:** Meta-analysis of overall survival. HR: Hazard ratio; CI: Confidence interval.

Figure 4: Meta-analysis of progression-free survival with thalidomide.

Table 2: Results of sensitivity analyses

Studies omitted	OS			PFS		
	HR	95% CI	I² (%)	HR	95% CI	I² (%)
Facon 2007	0.88	0.76–1.02	23	0.69	0.61–0.78	11
Hulin 2009	0.84	0.73–0.98	48	0.66	0.58–0.74	44
Palumbo 2008	0.78	0.68–0.90	40	0.65	0.58–0.74	45
Waage 2010	0.76	0.66–0.89	27	0.59	0.52–0.67	0
Sacchi 2011	0.84	0.73–0.95	46	0.66	0.58–0.74	42
Beksac 2010	0.82	0.71–0.94	53			
Wijermans 2010	0.82	0.71–0.96	53	0.65	0.58–0.73	45

HR: Hazard ratio; OS: Overall survival; PFS: Progression-free survival; CI: Confidence interval.

Table 3: Grade 3 and 4 adverse events

MPT versus MP	Heterogeneity	Conclusion
Total events		
RR = 2.30	I² = 45%	MP is better than MPT
95% CI: 1.97–2.70	P = 0.120	
P<0.00001		
Thrombosis or embolism		
RR = 2.33	I² = 46%	MP is better
95% CI: 1.55–3.51	P = 0.080	
P = 0.0001		
Peripheral neuropathy		
RR = 5.88	I² = 3%	MP is better
95% CI: 3.35–10.32	P = 0.400	
P<0.00001		
Rash		
RR = 4.87	I² = 3%	MP is better
95% CI: 1.07–22.09	P = 0.680	
P = 0.040		
Infection		
RR = 2.00	I² = 28%	MP is better
95% CI: 1.39–2.87	P = 0.240	
P = 0.002		

MPT: Melphalan, prednisone, and thalidomide; MP: Melphalan and prednisone; RR: Risk ratio; CI: Confidence interval.

As suggested in Table 3, use of MPT was associated with a statistically significant risk for thrombosis or embolism (RR = 2.33, 95% CI: 1.55–3.51; P = 0.0001). A further sub-group analysis showed that the incidence of thrombotic-embolism events decreased significantly after the introduction of prophylactic anticoagulation [Figure 5].

Although the serious adverse events appeared after the addition of thalidomide, there was a statistically nonsignificant difference in treat-related morality (TRM; RR = 1.24, 95% CI: 0.95–1.63; P = 0.12) between MPT and MP groups [Figure 6].

DISCUSSION

In the 1960s, the classic MP combination was born when a trial of 183 patients with melphalan versus MP demonstrated a survival improvement by 6 months in MP arm.[18] With the progress, myeloablative doses of melphalan with stem-cell rescue further improved median OS, and consequently became the most acceptable management strategy for transplant eligible patients.[3,19,20] Other regimens also demonstrated a higher response such as thalidomide combination with dexamethasone used in relapsed and refractory MM.[5,21,22]

However, elderly patients are particularly susceptible to drug-related side effects. Six phase III trials comparing efficacy of MP with MPT in transplant-ineligible, elderly patients conducted in the European Union have showed conflicting conclusions which made the interpretation difficult, especially the impact on PFS and OS. Meta-analysis helps clarify the impact of thalidomide on the OS of previously untreated patients with myeloma. However, reviews conducted in these years yielded inconsistent results. This meta-analysis identified 7 trials of thalidomide for previously untreated myeloma. Pooling these survival data enabled us to increase the power of the analysis and confirmed that thalidomide confers a significant survival advantage among these patients.

OS data were available for seven trials.[11-17] PFS were available from other six trials.[11-13,15-17] Sub-group and sensitivity analysis was performed to detect studies leading to significant heterogeneity in our analysis. OS was significantly improved with an HR of 0.82 in favor of thalidomide-based regimen. The integrated efficacy analysis also indicated a strong trend toward improved PFS. As meta-analysis analyzes studies that are diverse both clinically and methodologically, heterogeneity in the outcomes is not unexpected. When Facon et al.[12] or Waage et al.[16] study was excluded from the analysis, the heterogeneity across trials became insignificant for both
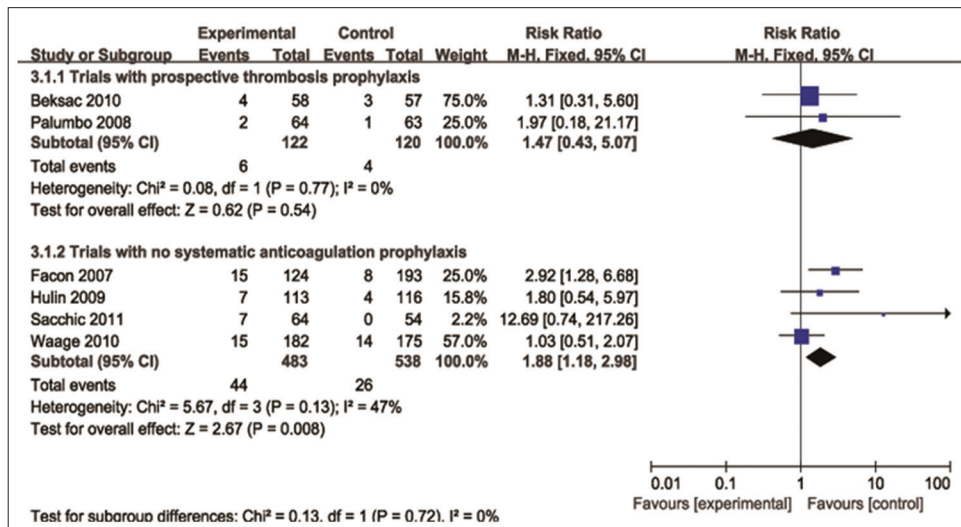
Figure 5: Sub-group analysis of the incidence of thrombosis or embolism events with prophylactic anticoagulation.
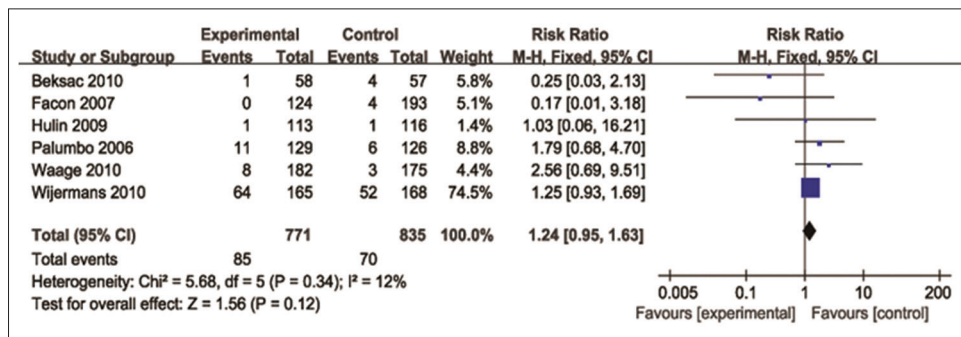

Figure 6: Meta-analysis of adverse events-related mortality.

PFS and OS outcomes [Table 2]. Thirty percentage of the patients in Waage *et al*.[16] study had WHO performance status 3 or 4 compared with 6–8% in the other studies. The higher proportion of patients with WHO performance status more than 3 might explain one of the sources of the heterogeneity. Patients eligible for inclusion into Facon *et al*.[12] trial were aged between 65 and 75 years. Patients younger than 65 years were included if they were ineligible for high-dose treatment. Sensitivity analysis suggested that age and performance status of patients might reflect the treatment efficacy of thalidomide-based regimen. More studies and sub-group analysis should conduct to clarify it.

In addition, our meta-analysis suggests significant and consistent relative improvement in response rates with the addition of thalidomide. Although a higher incidence of grade 3 or 4 adverse events was observed in the MPT arms, there was a statistically nonsignificant difference in TRM. VTE is a known adverse effect of thalidomide. Although no anticoagulation prophylaxis was given initially in all the included trials, Palumbo *et al*.[4,11] and Beksac *et al*.[14] study protocols were revised to include prophylaxis against VTE subsequently. After the introduction of anticoagulation prophylaxis, grade 3 or 4 thromboembolism was reduced. Sub-group analysis showed prophylactic anticoagulation

may decrease the *RR* of VTE with induction thalidomide. This result is different from that reported before.[6] The latter study included induction or maintenance thalidomide at any dose, for any duration, as monotherapy, or in combination with corticosteroid or chemotherapy.

Our meta-analysis was based on trials reported in the literature. As such, there are a number of limitations of this meta-analysis. The quality of a meta-analysis is always subject to the quality of included studies. All of the 7 trials in English included in this meta-analysis were moderate to large RCTs. As well, our analyses were limited to the data presented and/or shared by authors of the source studies. In some cases, we had incomplete information.

Despite the limitations of our study, we believe that it makes an important contribution to the myeloma field. Before our meta-analysis, Fayers *et al*.[23] performed an individual patient meta-analysis and demonstrated that thalidomide added to MP improves survival in previously untreated elderly patients with MM. Kapoor *et al*.[8] compared efficacy of MPT with MP by pooling results on *RR*, PFS, and OS. Six prospective RCTs with data extractable from five published trials (*n* = 1568) were identified. It is important to reach a definitive conclusion based on all available trial data. Our robust and update outcome data allow us to state

that thalidomide regimen seems to have superior outcome than nonthalidomide regimen although at a cost of greater toxicity. In addition, our review showed that VTE risk may be incompletely abrogated by anticoagulation prophylaxis, age or performance status may be one of the factors that affect survival of patients used MPT regimen. Further trials are required to clarify this issue. Based on these data, MPT regimen might be a category 1 primary treatment in transplant-ineligible patients with MM, especially for those who do not have access to novel agents.

In conclusion, MPT can be considered one of the standards of care for elderly and/or transplant-ineligible MM patients. Randomized trials comparing other new combination regimens with MPT, such as lenalidomide or bortezomib, would further advance the field for such patients.

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Conflicts of interest

There are no conflicts of interest.

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