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Original Article

Thalidomide-dexamethasone-based induction treatment before autologous stem-cell transplantation for untreated multiple myeloma: a meta analysis

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Abstract: A meta-analysis was performed to compare the efficacy and safety of thalidomide-dexamethasone-based (TD-based) versus dexamethasone-based (D-based) induction treatment before autologous stem-cell transplantation (ASCT) in patients with previously untreated multiple myeloma (MM). Overall, five RCTs involving 2746 patients were included. Compared with D-based regimens, TD-based regimens significantly improved pre-ASCT complete response rate (CR) (OR 1.52, 95% CI 1.12-2.06), pre-ASCT overall response rate (ORR) (OR 1.92, 95% CI 1.57-2.35), post-ASCT CR (OR 1.44, 95% CI 1.14-1.81), post-ASCT ORR (OR 1.41, 95% CI 1.04-1.92) as well as progression-free survival (PFS) (HR 0.73, 95% CI 0.59-0.91), but not overall survival (OS) (HR 0.91, 95% CI 0.80-1.04). The risk of venous thromboembolism (VTE) with grade 3 or higher with TD-based regimens was significantly higher relative to D-based regimens (OR 1.84, 95% CI 1.36-2.48). By pooling data from the trials that administered VTE prophylaxis, we found that the risk of VTE with grade 3 or higher with VTE prophylaxis was lower than when there was no VTE prophylaxis in the protocol, but was still significantly elevated relative to D-based regimens (OR 1.54, 95% CI 1.05-2.27). In summary, our meta-analysis demonstrated that in patients with previously untreated multiple myeloma, TD-based induction treatment before ASCT results in significantly improved response rates (pre-ASCT CR, pre-ASCT ORR, post-ASCT CR and post-ASCT ORR) and PFS with a trend towards improvement in OS compared with D-based regimens, but at a cost of higher risk of VTE with grade 3 or higher.

Keywords: Autologous stem-cell transplantation, dexamethasone, multiple myeloma, meta-analysis, thalidomide

Introduction

Multiple myeloma (MM) is the second most common hematologic malignancy. It is a plasma cell malignancy characterized by clonal proliferation of plasma cells in the bone marrow and accompanied by the secretion of monoclonal protein in the blood and/or urine [1]. High-dose treatment followed by autologous stem-cell transplantation (HDT/ASCT) has become first-line treatment in patients eligible for transplantation. In the context of HDT/ASCT, the achievement of complete remission (CR) or very good partial remissions (VGPR) is an important prognostic factor for prolonged PFS and OS [2, 3]. Induction therapy is one strategy to improve the CR plus VGPR rate in the HDT/ASCT paradigm [4]. Before the era of novel drugs, induction therapy typically consisted of high-dose dexamethasone alone or combined with vincristine and doxorubicin. The activity of vincristine-doxorubicin-dexamethasone (VAD) mainly depends on the high-dose dexamethasone. Thalidomide is an oral, immunomodulatory drug. It has activity as induction therapy [5]. Moreover, it produces little hematologic stem-cell toxicity, which likely has less impact on the collection of stem cells for ASCT [6]. The demonstrated activity and little hematologic stem-cell toxicity of thalidomide provide a rationale for its use as a component of induction treatment for transplant-eligible patients with previously untreated multiple myeloma.

The goal of this meta-analysis was to compare the efficacy and safety of thalidomide-dexa-

Table 1. Search criterion of Medline (via PubMed, from inception to March 12, 2015)

No.	Query Results	Results
#19	Search ((((((((((myeloma [Title/Abstract]) OR myelom*[Title/Abstract]) OR multiple myeloma [Title/Abstract]) OR plasmacytoma [Title/Abstract]) OR plasmocytom* [Title/Abstract])) OR "Multiple Myeloma" [Mesh])) AND ((thalidomide [Title/Abstract]) OR "Thalidomide" [Mesh])) AND ((((((((((Randomized Controlled Trial[Publication Type]) OR controlled clinical trial [Publication Type]) OR randomized [Title/Abstract]) OR placebo [Title/Abstract]) OR clinical trials as topic [MeSH Terms]) OR randomly [Title/Abstract]) OR trial [Title/Abstract])) AND humans [MeSH Terms])) AND ((dexamethasone [Title/Abstract]) OR "Dexamethasone" [Mesh])	320
#18	Search (((((((((Randomized Controlled Trial [Publication Type]) OR controlled clinical trial [Publication Type]) OR randomized [Title/Abstract]) OR placebo [Title/Abstract]) OR clinical trials as topic [MeSH Terms]) OR randomly [Title/Abstract]) OR trial [Title/Abstract])) AND humans [MeSH Terms]	928216
#17	Search humans [MeSH Terms]	13671252
#16	Search trial [Title/Abstract]	385185
#15	Search randomly [Title/Abstract]	229102
#14	Search clinical trials as topic [MeSH Terms]	283304
#13	Search placebo [Title/Abstract]	164398
#12	Search randomized [Title/Abstract]	338554
#11	Search controlled clinical trial [Publication Type]	88478
#10	Search Randomized Controlled Trial [Publication Type]	383186
#9	Search (dexamethasone [Title/Abstract]) OR "Dexamethasone" [Mesh]	59533
#8	Search dexamethasone [Title/Abstract]	45480
#7	Search "Dexamethasone" [Mesh]	44371
#6	Search (thalidomide [Title/Abstract]) OR "Thalidomide" [Mesh]	8699
#5	Search thalidomide [Title/Abstract]	6444
#4	Search "Thalidomide" [Mesh]	6716
#3	Search ((((((myeloma [Title/Abstract]) OR myelom* [Title/Abstract]) OR multiple myeloma [Title/Abstract]) OR plasmacytoma [Title/Abstract]) OR plasmocytom* [Title/Abstract])) OR "Multiple Myeloma" [Mesh]	59919
#2	Search ((((myeloma [Title/Abstract]) OR myelom* [Title/Abstract]) OR multiple myeloma [Title/Abstract]) OR plasmacytoma [Title/Abstract]) OR plasmocytom* [Title/Abstract]	53073
#1	Search "Multiple Myeloma" [Mesh]	32368

methasone-based with dexamethasone-based regimens as induction therapy in transplant-eligible patients with previously untreated multiple myeloma.

Materials and methods

Data sources and search strategy

We searched databases including PubMed, Embase, and the Cochrane Library. The search criterion of all three databases was listed in **Tables 1**-**3**, respectively. Additionally potentially eligible studies were examined from the reference lists of all included trials. No language restrictions were applied. The last search was updated to 12 March 2015.

Selection criteria

We included phase 3 randomized, controlled clinical trials comparing TD-based with D-based induction regimens before ASCT for patients with previously untreated multiple myeloma. We also required trials to definitely provide sufficient information including the therapeutic methods and outcomes. Data extraction and analysis were performed by two independent reviewers.

Outcome measures

The primary outcome for our meta-analysis was CR and PFS. Secondary outcomes included ORR, OS and VTE. The response to treatment was evaluated according to the European Group for Blood and Marrow Transplantation Criteria [7] or the International Myeloma Working Group Uniform Response Criteria [8]. PFS was calculated from randomization until progression or relapse. OS was measured from randomization until death from any cause. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria.

Study quality assessment

All studies were phase 3 randomized controlled trials. The methodological quality of the included studies was assessed by two reviewers using the following criteria: (1) allocation gen-

Table 2. Search criterion of Embase (from inception to March 12, 2015)

No.	Query Results	Results
#24	Search #7 and #10 and #13 and #23	1595
#23	Search #21 and #22	1387060
#22	Search 'human'/exp	15590498
#21	Search #14 or #15 or #16 or #17 or #18 or #19 or #20	1629760
#20	Search trial: ab, ti	511923
#19	Search randomly: ab, ti	282268
#18	Search 'clinical trial'/exp	1004642
#17	Search placebo: ab, ti	213171
#16	Search randomized: ab, ti	447953
#15	Search 'controlled clinical trial'/exp	480184
#14	Search 'Randomized Controlled Trial'/exp	360176
#13	Search #11 or #12	123536
#12	Search 'dexamethasone'/exp	114801
#11	Search dexamethasone: ab, ti	56654
#10	Search #8 or #9	22960
#9	Search 'thalidomide'/exp	22005
#8	Search thalidomide: ab, ti	9846
#7	Search #1 or #2 or #3 or #4 or #5 or #6	85308
#6	Search 'multiple myeloma'/exp	54196
#5	Search plasmocytom*: ab, ti	1885
#4	Search plasmacytoma: ab, ti	5567
#3	Search 'multiple myeloma': ab, ti	39102
#2	Search myelom*: ab, ti	66878
#1	Search myeloma: ab, ti	54816

eration, (2) allocation concealment, (3) double blind, (4) data analyses, (5) descriptions of dropouts.

Publication bias

Given the small numbers of trials included in this meta-analysis, publication bias was not formally assessed.

Statistical analysis

We used STATA (version 11.0; StataCorp) software for all meta-analyses. The hazard ratio (HR) and 95% confidence interval (95% CI) were used to evaluate time-to-event outcomes (PFS, OS). When not available from the trials, the HR was estimated using methods described by Tierney et al. [9]. The odd risk (OR) and 95% CI were used to evaluate dichotomous outcomes (CR, ORR, VTE). The heterogeneity was analyzed by the chi-squared test and considered statistically significant when the p value was less than 0.1 or the I^2 was greater than 50% [10]. A fixed effect model was used for outcomes without heterogeneity. A random-effect model was used when the heterogeneity was considered statistically significant. A sensitivity analysis was performed to explore the possible sources of heterogeneity.

Results

Description of trials

Our search strategy initially generated 2103 references through a comprehensive search of PubMed, Embase, and the Cochrane Library. Among them, 409 were duplicated and 1666 were excluded on title and abstract. The remaining 28 studies were evaluated in detail. Finally, five RCTs [4, 6, 11-13] meet all the inclusion criteria and were included in our study (**Figure 1**). **Table 4** outlines the characteristics of the five trials involving a total of 2746 patients included in our study. All these trials were conducted between 2007 and 2012. The sample size ranged from 232 to 1111. Four trials [6, 11-13] used VTE prophylaxis.

Methodological quality of the trials

The methodological quality of each study is illustrated in **Table 5**. None of the included trials reported the methods of sequence generation. Only one trial [6] described the method of allocation concealment. None of the included trials were double blinded. All trials reported intention-to-treat (ITT) analyses (the Morgan trial used ITT analysis for response rate and used per-protocol analysis for PFS and OS). All trials adequately described dropout rates.

Complete response rates and overall response rates

Data on pre-ASCT CR and ORR were available in four of all five trials, while data on post-ASCT CR and ORR were available in three of all five trials. The weighted OR for pre-ASCT and post-ASCT

Table 3. Search criterion of Cochrane Library (from inception to March 12, 2014)

No.	Query Results	Results
#1	"myeloma": ti, ab, kw or "myelom*": ti, ab, kw or "multiple myeloma": ti, ab, kw or "plasmacytoma": ti, ab, kw or "plasmocytom*": ti, ab, kw (Word variations have been searched)	2408
#2	MeSH descriptor: [Multiple Myeloma] explode all trees	892
#3	#1 or #2	2408
#4	thalidomide: ti, ab, kw (Word variations have been searched)	761
#5	MeSH descriptor: [Thalidomide] explode all trees	354
#6	#4 or #5	761
#7	dexamethasone: ti, ab, kw (Word variations have been searched)	4901
#8	MeSH descriptor: [Dexamethasone] explode all trees	2410
#9	#7 or #8	4907
#10	#3 and #6 and #9	188

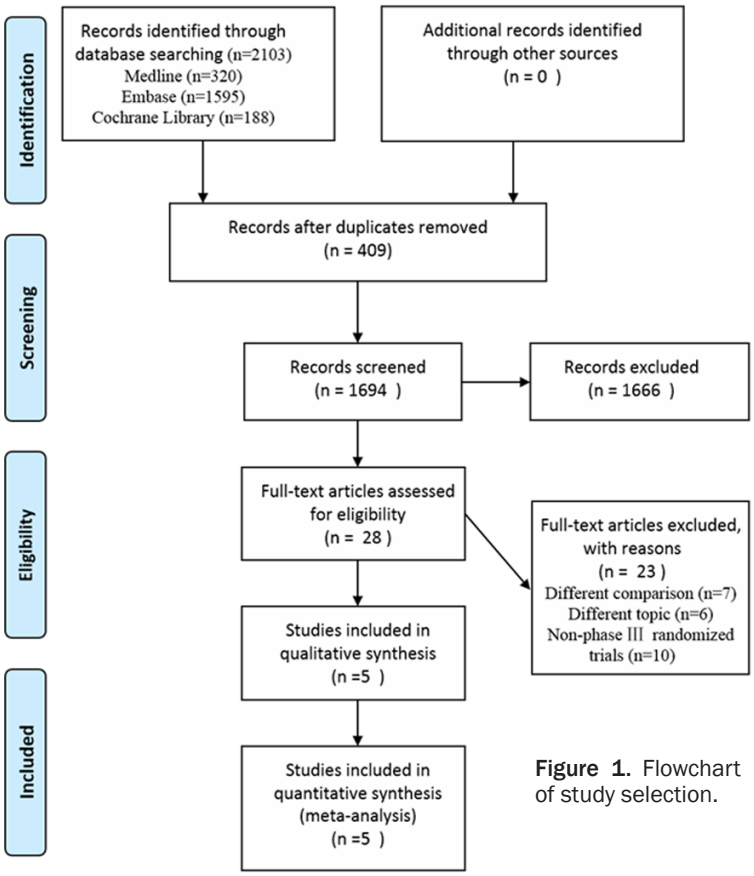

Figure 1. Flowchart of study selection.

CR were 1.52 (95% CI 1.12-2.06, **Figure 2A**) and 1.44 (95% CI 1.14-1.81, **Figure 2B**), respectively, in favor of TD-based induction regimens. The weighted OR for pre-ASCT and post-ASCT ORR were 1.92 (95% CI 1.57-2.35, **Figure 3A**) and 1.41 (95% CI 1.04-1.92, **Figure 3B**), respectively, indicating that TD-based induction regimens were significantly more effective than D-based induction regimens in achieving pre-ASCT ORR and post-ASCT ORR.

Progression-free survival and overall survival

Data on PFS and OS were extracted from four of all five trials (Moreau et al.' trial was not designed to analyze survival). The weighted HR for PFS and OS were 0.73 (95% CI 0.59-0.91, **Figure 4**) and 0.91 (95% CI 0.80-1.04, **Figure 5**), respectively, indicating that TD-based induction regimens significantly improved PFS, but this did not translate into an evident benefit in OS.

Venous thromboembolism with grade 3 or higher

Venous thromboembolism is a well-known adverse effect of thalidomide [14-16]. Data on VTE with grade 3 or higher was extracted from four of all five trials (Morgan et al.' trial only reported VTE with all grades). The weighted OR for VTE with grade 3 or higher were 1.84 (95% CI 1.36-2.48, **Figure 6A**), in favor of D-based induction regimens. Three of the four trials administered VTE prophylaxis (except Moreau et al.' trial). To estimate the risk of VTE with grade 3 or higher with TD-based induction regimens and VTE prophylaxis, we pooled data from the trials that administered VTE prophylaxis. As shown in **Figure 6B**, the risk of VTE with grade 3 or higher was lower than when there was no VTE prophylaxis in the protocol, but was still significantly elevated rel-

Table 4. Characteristics of included trials

Author [Year]	NO. of patients	Age, Median (range)	Median follow-up (Months)	Intervention	VTE prophylaxis
Zervas [2007]	Expt: 117 Ctrl: 115	Expt: 62.5 (40-73) Ctrl: 64 (35-74)	24	Expt: thalidomide + vincristine + liposomal doxorubicin + dexamethasone Ctrl: vincristine + liposomal doxorubicin + dexamethasone	LMWH or aspirin
Barlogie [2008]	Expt: 323 Ctrl: 345	Age ≥65 year Expt: 20% Ctrl: 21%	72	Expt: total therapy 2 + thalidomide Ctrl: total therapy 2	LMWH
Lokhorst [2010]	Expt: 268 Ctrl: 268	Expt: 57 (30-65) Ctrl: 56 (32-65)	52	Expt: thalidomide + doxorubicin + dexamethasone Ctrl: vincristine + doxorubicin + dexamethasone	LMWH
Moreau [2011]	Expt: 100 Ctrl: 99	Expt: 58 (54-62) Ctrl: 57 (52-61)	32	Expt: thalidomide + bortezomib + dexamethasone Ctrl: bortezomib + dexamethasone	No
Morgan [2012]	Expt: 555 Ctrl: 556	Expt: 59 (33-78) Ctrl: 59 (31-74)	47	Expt: thalidomide + cyclophosphamide + dexamethasone Ctrl: cyclophosphamide + vincristine + doxorubicin + dexamethasone	LMWH, warfarin, or aspirin

LMWH, low molecular weight heparin; VTE, venous thromboembolism.

Table 5. Methodological quality assessment of included trials

Author [Year]	Allocation generation	Allocation concealment	Double blind	Data analysis	Descriptions of dropouts
Zervas [2007]	Unclear	Unclear	Unclear	ITT	Yes
Barlogie [2008]	Unclear	Unclear	Unclear	ITT	Yes
Lokhorst [2010]	Unclear	Unclear	Unclear	ITT	Yes
Moreau [2011]	Unclear	Unclear	Open-label	ITT	Yes
Morgan [2012]	Unclear	Adequate	Unclear	ITT/PP	Yes

ITT, intention-to-treat; PP, per-protocol.

ative to D-based induction regimens (OR 1.54, 95% CI 1.05-2.27).

Heterogeneity and sensitivity analysis

Among all analyses, statistically significant heterogeneity was observed in PFS (I^2=74.6%, P=0.008). Sensitivity analysis suggested that the Morgan et al.' study was the source of this statistical heterogeneity (**Figure 7**). The Morgan et al.' study was the only trial using per-protocol analysis for PFS. More importantly, control arm in this trial contain four agents (dexamethasone, cyclophosphamide, vincristine, and doxorubicin) while experiment arm only contain three agents (thalidomide, dexamethasone, and cyclophosphamide). Exclusion of the Morgan study resulted in greater benefit in PFS (HR 0.66, 95% CI 0.58-0.76) and made heterogeneity non-significant (I^2=0.0%, P=0.931) (**Figure 8**).

Discussion

Preclinical data suggests that thalidomide overcome drug resistance of MM cells to dexamethasone by inducing apoptosis and G1 growth arrest. Moreover, thalidomide enhances the anti-MM activity of dexamethasone [17, 18]. These data provided the rationale for combination thalidomide with dexamethasone. Indeed, the combination regimens containing thalidomide and dexamethasone as salvage treatment appears effective in patients with refractory MM [19-21]. Several studies reported that the combination thalidomide with dexamethasone induced a high response rate and low risk of serious irreversible toxicity in patients with previously untreated MM [22, 23]. Moreover, thalidomide as induction therapy before ASCT for patients with previously untreated MM produced little hematologic stem-cell toxicity. These merits support further studies of the regimens containing thalidomide and dexamethasone as induction therapy before ASCT for patients with previously untreated MM. However, it remains controversial that whether transplant-eligible patients will benefit more from TD-based induction therapy compared to D-based induction therapy because of the inconsistent results across phase 3 RCTs. We performed a meta-analysis in an attempt to gain further insight into the benefits and risks of TD-based regimens.

Our meta-analysis demonstrated TD-based regimens as induction therapy before ASCT improves pre-ASCT CR, post-ASCT CR, pre-ASCT ORR, post-ASCT ORR and PFS in patients with previously untreated MM. PFS improve-

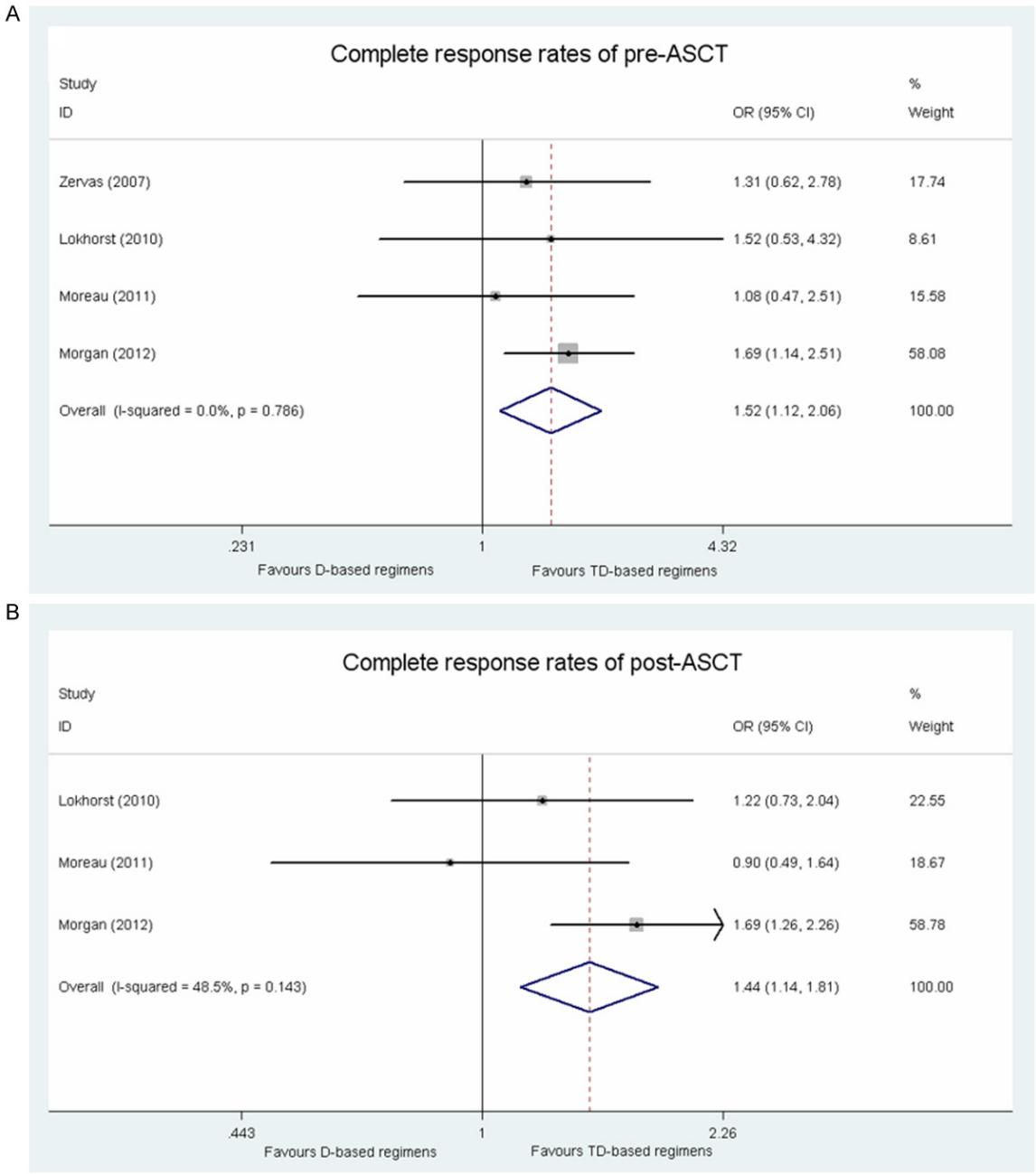

Figure 2. Forest plots from a meta-analysis of complete response rates with induction regimens (A). Pre-ASCT complete response rate (B). Post-ASCT complete response rate. OR, Odds ratio; CI, 95% confidence interval.

ment was consistent in three studies of the four trials that estimated PFS. Another one study did not show a PFS advantage of TD-based regimen. One explanation was that the combination therapy of four agents was used in D-based arm while only three drugs in TD-based arm. Another explanation was that this study used per-protocol analysis for PFS. Our study also showed a strong trend toward improved OS with TD-based versus D-based induction. Given that median survival for transplant-eligible patients with MM has been estimated as 7 to 8 years, longer follow-up should be required to evaluate the OS benefit [24, 25].

In addition to efficacy, safety is an equally important consideration for whether to subject patients to TD-based induction therapy.

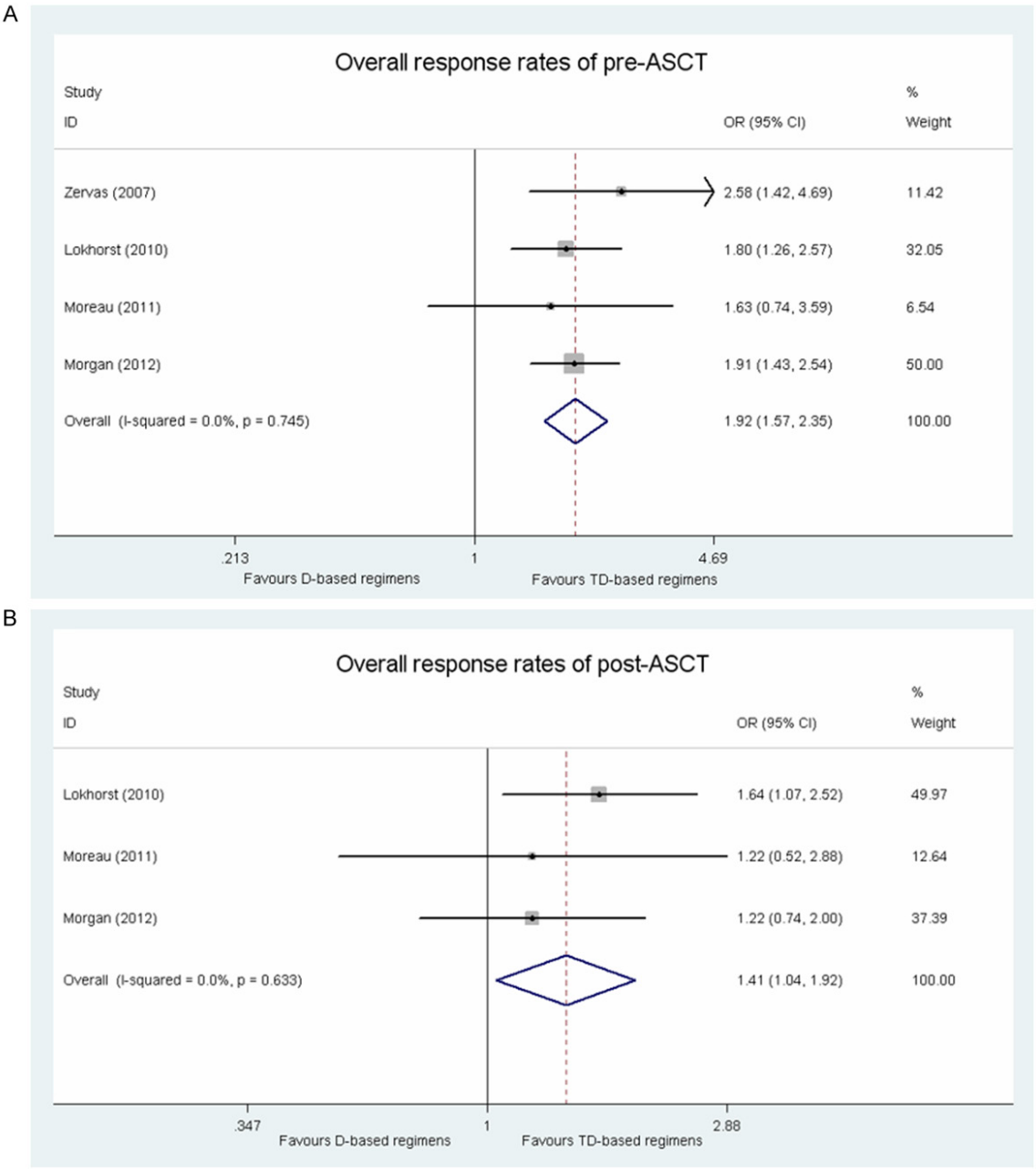

Figure 3. Forest plots from a meta-analysis of overall response rates with induction regimens (A). Pre-ASCT overall response rate (B). Post-ASCT overall response rate. OR, Odds ratio; CI, 95% confidence interval.

Previous studies showed the use of thalidomide was associated with increased risk of VTE. Of the four trials that reported VTE of grade 3/4, the Barlogie trial reported a significantly higher risk of VTE with grade 3/4 in the TD-based arm, while the TD and D-based arms did not differ significantly in the risk of VTE with grade 3/4 in the other three trials. Pooled data from these trials showed a significantly increased risk of TD-based regimens for VTE with grade 3 or higher. To estimate the risk of VTE with TD-based induction therapy and VTE prophylaxis, we pooled data from the studies that administered VTE prophylaxis. The pooled data showed that the risk of VTE with grade 3 or higher with VTE prophylaxis was lower than when there was no VTE prophylaxis in the protocol, but was still significantly elevated relative

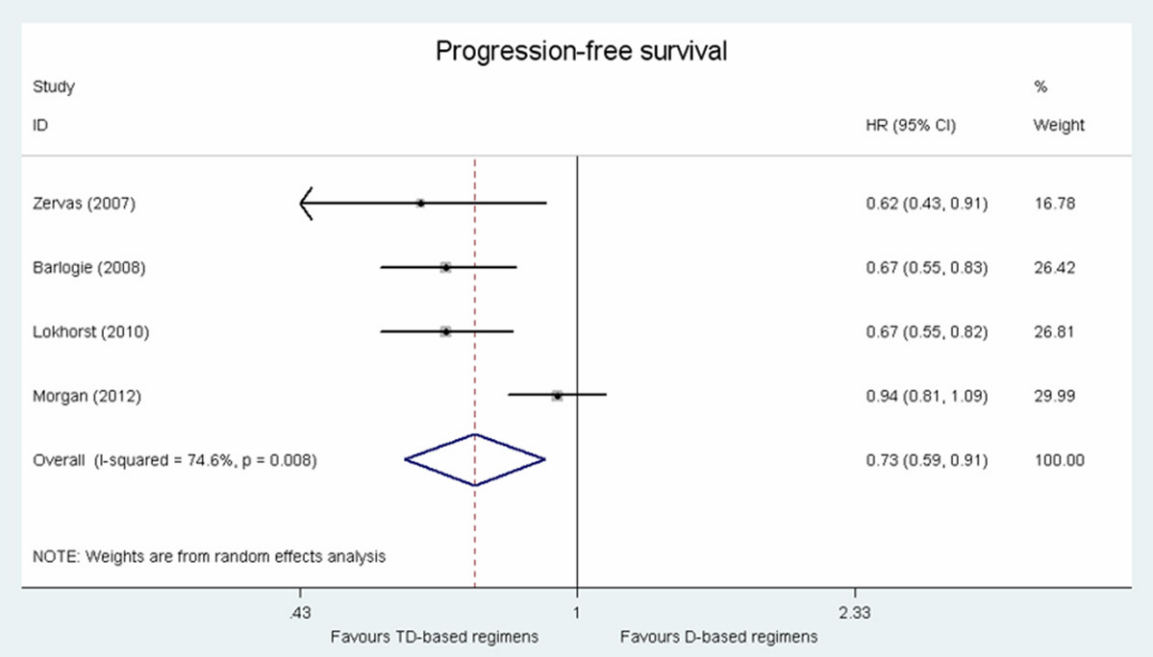

Figure 4. Individual trials and overall hazard ratios for progression-free survival in the comparison of TD-based and D-based regimens. HR, Hazard ratio; CI, 95% confidence interval.

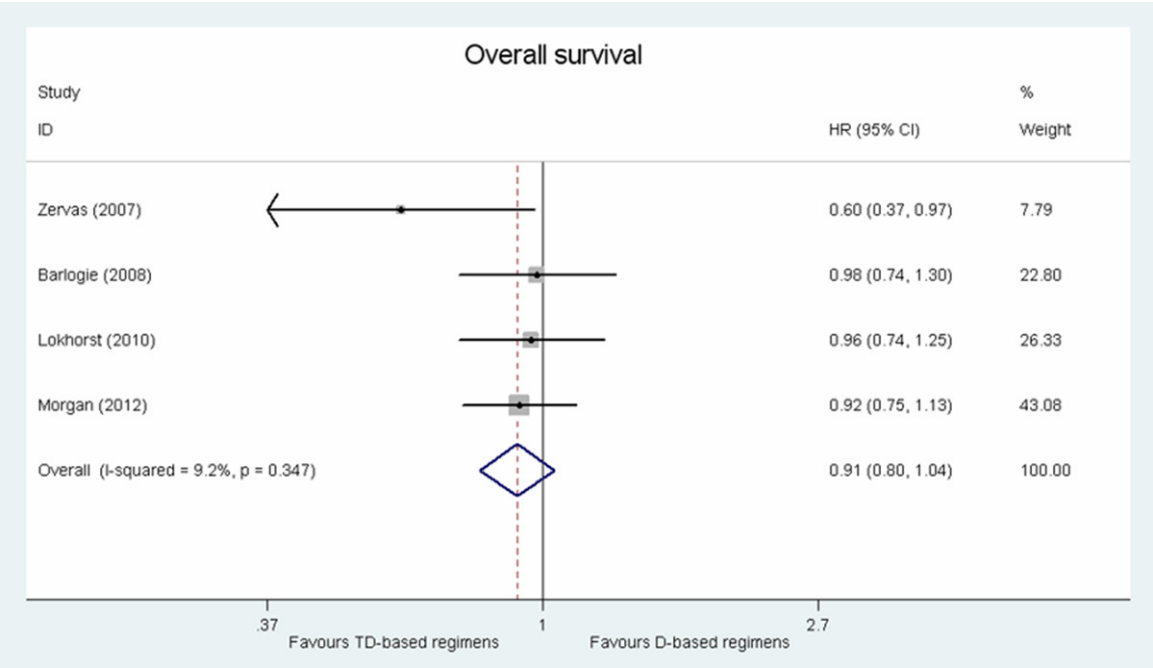

Figure 5. Individual trials and overall hazard ratios for overall survival in the comparison of TD-based and D-based regimens. HR, Hazard ratio; CI, 95% confidence interval.

to D-based regimens. These results seemed be consistent with Hicks study that showed the risk of VTE decreased but not disappeared after VTE prophylaxis was used in patients treated with thalidomide. Zangari trial [14] reported that VTE developed in 14 of 50 patients treated with thalidomide but in only 2 of 50 patients not receiving the agent. In their

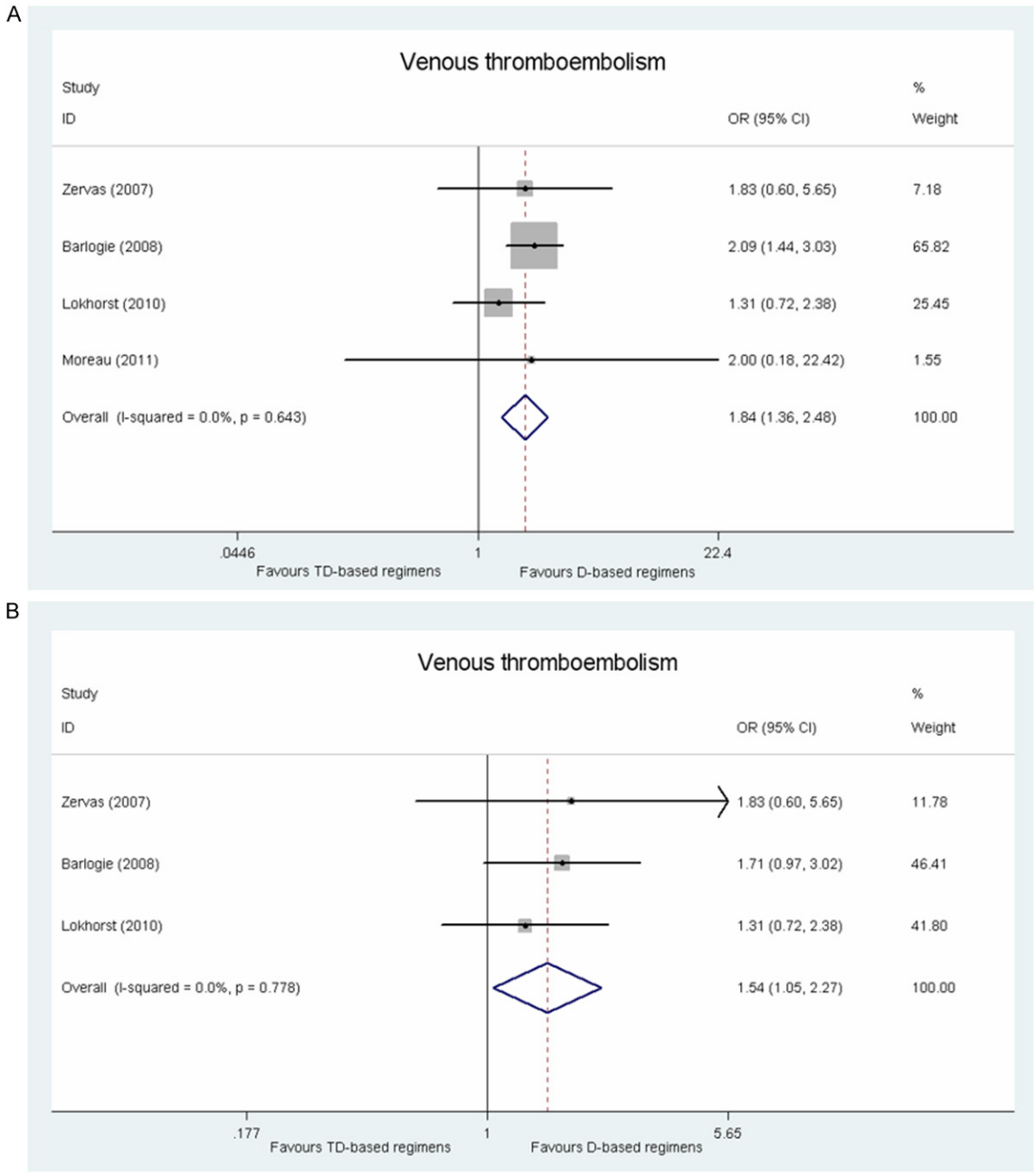

Figure 6. Individual trials and overall odds ratios for the incidence of venous thromboembolism in the comparison of TD-based and D-based regimens. OR, Odds ratio; CI, 95% confidence interval.

trial, administration of thalidomide was resumed in 75% of patients given VTE prophylaxis. However, given none of the trials included in our study were designed to randomly assess VTE prophylaxis, RCTs that randomly assess VTE prophylaxis should be needed to verify these results.

There are some limitations of our study: (1) Our work was based on aggregate study, not on analysis of individual patient data, and is therefore limited in time-to-event analyses. (2) Trials included in our study were heterogeneous in induction treatment regimen, and the differences of maintenance therapy between the trials likely confound the effects of induction treatment on efficacy and safety outcomes. Nevertheless, no heterogeneity was observed in most analyses. (3) The quality of a meta-analysis is always subject to the quality of

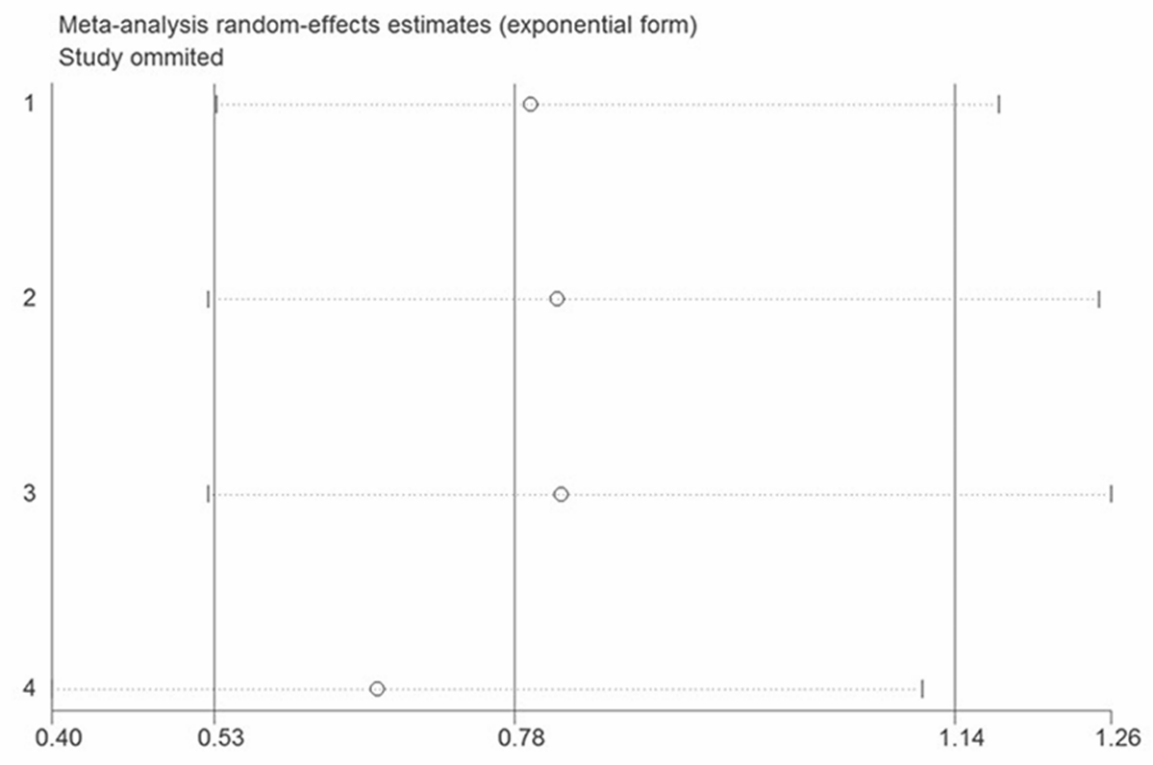

Figure 7. A sensitivity analysis of the effect of a single study of induction regimens on the pooled progression-free survival.

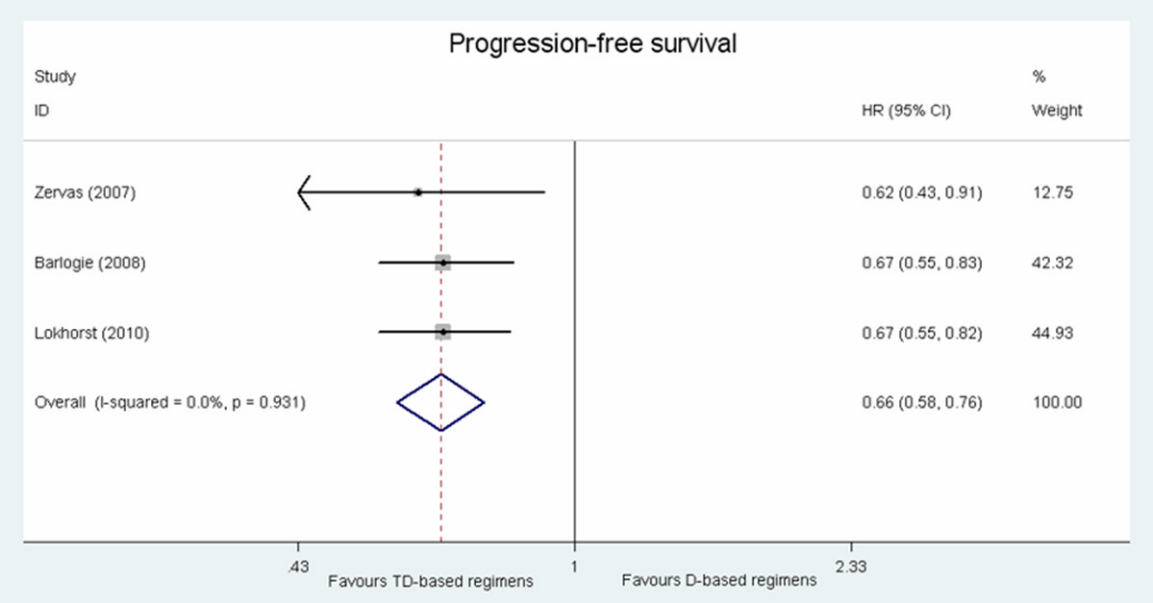

Figure 8. Forest plots from a meta-analysis of progression-free survival with induction regimens excluding the Morgan study. HR, Hazard ratio; CI, 95% confidence interval.

selected trials. All of the five trials included in our study were moderate to large RCTs that used intention-to-treat analysis (the Morgan trial used both ITT analysis and PP analysis), but only one trial adequately reported allocation concealment, and none were double blind-

ed. The absence of allocation concealment and blinding possibly had minimal effect on efficacy and safety outcomes.

In summary, our results showed that TD-based induction regimens before ASCT in patients with previously untreated myeloma had superior outcomes in terms of response rates (pre-ASCT CR, post-ASCT CR, pre-ASCT ORR and post-ASCT ORR) and PFS, compared to D-based induction regimens. Our study also showed a strong trend toward improved OS with TD-based versus D-based induction. However, potential risk of VTE should be taken into account.

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Disclosure of conflict of interest

None.

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