

Original Article

Combination therapy with lenalidomide and dexamethasone for multiple myeloma: a meta-analysis of phase III randomized controlled trials

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Abstract: Novel oral immunomodulatory drug lenalidomide has been proven to have significant clinical activity in multiple myeloma (MM). However, it is unclear whether patients with MM will benefit more from lenalidomide plus dexamethasone (LD) therapeutic strategy. Herein, our meta-analysis aims to evaluate the efficiency and safety of LD regimens for multiple myeloma. We searched PubMed, EMBASE, and the Cochrane Library using the terms “(lenalidomide or revlimid) AND dexamethasone AND multiple myeloma.” Four trials with 1969 patients were identified in total. LD regimens significantly improved complete response (CR) (OR = 5.38, 95% CI: 1.77 to 16.38), overall response rates (ORR) (OR = 3.75, 95% CI: 1.95 to 7.23), progression-free survival (PFS) (HR = 0.50, 95% CI: 0.25 to 0.97) as well as overall survival (OS) (HR = 0.73, 95% CI: 0.62 to 0.86). Most expected adverse effects of LD regimens, including hematologic (neutropenia, thrombocytopenia, anemia), nonhematologic (deep-venous thrombosis, infections, muscle weakness), were associated with an increased risk. However, several side effects such as fatigue and dyspnea were comparable in both groups. These results indicated that LD regimens might be a promising prospect in the frontline for patients with MM.

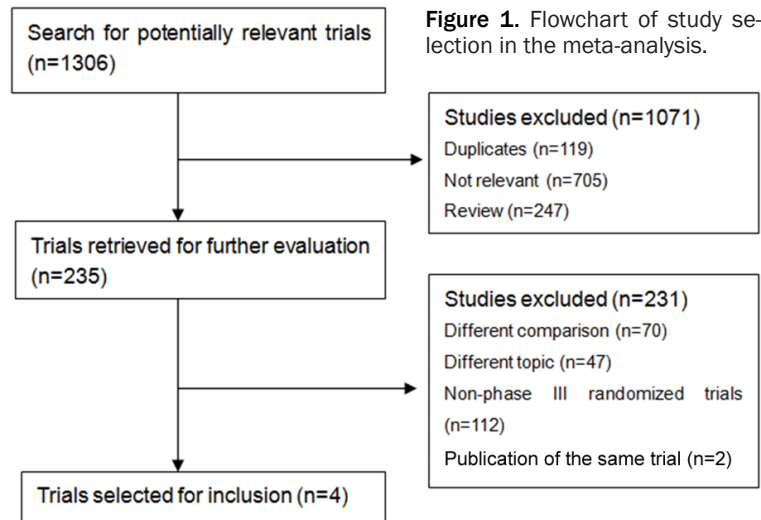
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Introduction

Multiple myeloma (MM) is a malignant disease characterized by proliferation of clonal plasma cells in the bone marrow and typically accompanied by the secretion of monoclonal immunoglobulins that are detectable in the serum or urine [1]. It is often associated with extensive skeletal destruction, infections, anemia, hypercalcemia, and renal failure [2]. Although MM remains incurable with a high incidence rate in the aged, the clinical outcomes have considerably improved as a result of novel achievable therapies in treatment. Together with high dose chemotherapy and autologous stem-cell transplantation, the use of novel drugs such as proteasome inhibitors and immunomodulators has increased the survival expectations of patients with MM substantially over the past decades [3-6]. Meanwhile, the introduction of new drugs

(thalidomide, bortezomib and lenalidomide) has made it possible to attain high response rates and very good quality responses with survival times and long-term disease control [6, 7]. Different kinds of therapeutic strategies and treatment combinations also have been applied to manage patients with MM. Nevertheless, the choice of optimal strategy remains an important challenge, which should be based on the evaluation of benefits and risks [8]. Therefore, it is urgent to shape the future of treatments for MM management.

Recent studies have demonstrated that treatment with the immunomodulatory drug thalidomide alone or in combination with other agents have improved survival, time to progression, and response rates [9-13]. However, the toxic effects of fatigue, peripheral neuropathy, constipation, and deep-vein thrombotic events



Materials and methods

Literature search strategy

We searched databases including PubMed, EMBASE, and the Cochrane central register of controlled trials, using the terms “(lenalidomide or revlimid) AND dexamethasone AND multiple myeloma”. Further, we attempted to identify other potentially relevant literature by searching the reference sections of pertinent articles for this review on-line and manually. No language restrictions

were applied. The last search was performed in March 2015.

Study selection

To be included in this review, studies were required to be phase III randomized, controlled clinical trials evaluating the therapeutic outcomes of lenalidomide plus dexamethasone for the treatment of patients with multiple myeloma. Studies were also required to definitely provide sufficient information including the treatment methods, and the definition and evaluation of therapeutic outcomes of interest regardless of publication date, status and language. Data extraction and analysis were performed by two independent investigators (LG and MJG).

Outcomes assessments

The primary endpoint was overall survival (OS). The secondary endpoints included progression-free survival (PFS), response rate and toxicity. The response of patients to treatment was defined according to the European Group for Blood and Marrow Transplantation Criteria in two trials (from Weber and Dimopoulos) [18] and the International Myeloma Working Group Uniform Response Criteria [19] in the other two trials (from Zonder and Benboubker). Adverse events were graded and recorded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events.

Statistical analysis

Meta-analysis was conducted using Stata (version 11.0; StataCorp). Evaluation of hazard

remain problematic [14]. Since most patients who receive these novel drugs or other chemotherapy still relapse, continuous studies on the most efficient combinations and the novel mechanisms of these drugs are needed.

Lenalidomide (Revlimid) is a derivative of thalidomide that has demonstrated to be significantly less toxic and more potent compared with thalidomide in the treatment of patients with MM. In patients with relapsed and refractory MM alone, lenalidomide can overcome drug resistance and is well tolerated, and in combination with dexamethasone results in fewer nonhematologic side effects than either agent alone in refractory MM [15, 16]. Therefore, several investigators studied on the combination of various novel regimens, i.e. lenalidomide and dexamethasone, which show different pharmacological effects. These preclinical/early clinical investigations have shown the promising results that lenalidomide plus dexamethasone induced significantly higher response rates, delayed time to progression and overall survival (OS) [15-17].

Based on the positive preliminary findings, some large, multicenter, randomized phase III clinical trials compared lenalidomide plus dexamethasone (LD) with other regimens treatments. In order to better understand the efficacy and safety of this combination therapy, we performed a meta-analysis of the currently available literature in which patients with MM received lenalidomide and dexamethasone as initial or salvage therapy.

Lenalidomide and dexamethasone in multiple myeloma

Table 1. Characteristics of included trials

Author [Year]	Inclusion criteria	No. of patients (% of male)	Age, mean (range)	Follow-up ^a (months)	Intervention
Weber [2007]	Patients who had received at least one previous therapy for MM	Expt: 177 (59.9) Ctrl: 176 (59.1)	Expt: 64 (36-86) Ctrl: 62 (37-85)	17.6	Expt: L 25 mg on d 1-21 of a 28-d cycle + D 40 mg on d 1-4, 9-12, 17-20 for 4 cycles, Then D 40 mg only on d 1-4 Ctrl: D the same with that in LD arm
Dimopoulos [2007]	RRMM, received at least one previous therapy	Expt: 176 (59.1) Ctrl: 175 (58.9)	Expt: 63 (33-84) Ctrl: 64 (40-82)	16.4	Expt: L 25 mg on d 1-21 of a 28-d cycle + D 40 mg on d 1-4, 9-12, 17-20 for 4 cycles, Then D 40 mg only on d 1-4 Ctrl: D the same with that in LD arm
Zonder [2010]	Untreated multiple myeloma patients	Expt: 97 (55) Ctrl: 95 (58)	≥ 65 years old Expt: 49%/Ctrl: 47%	47.2	Expt: Induction: L 25 mg/d for 28 days + D 40 mg/d on d 1-4, 9-12, 17-20 for 35-day cycle. Maintenance: L 25 mg/d for 21 days + D 40 mg/d on d 1-4, 15-18 Ctrl: D the same with that in LD arm
Benboubker [2014]	Patients with newly diagnosed MM ineligible for transplantation	Expt: 535 (55) Ctrl: 547 (52)	Expt: 73 (44-91) Ctrl: 73 (51-92)	37.0	Expt: L 25 mg on d 1-21 of a 28-d cycle + D 40 mg on d 1, 8, 15, 22 Ctrl: M 0.25 mg/kg on d 1-4 + P 2 mg/kg on d 1-4 + T 200 mg in 42-day cycles

MM: multiple myeloma; RRMM: relapsed or refractory multiple myeloma; L: lenalidomide; D: dexamethasone; M: melphalan; P: prednisone; T: thalidomide; ^aMedian follow-up time (months).

Table 2. Methodological quality assessment of included trials

Author [Year]	Location	Multi-center	Allocation generation	Allocation concealment	Blind	Data analysis	Drop-out
Weber [2007]	United States, Canada	Yes	Computer generated	Adequate	Double blinded	ITT	N/A
Dimopoulos [2007]	Europe, Israel, Australia	Yes	Unclear	Unclear	Double blinded	ITT	N/A
Zonder [2010]	United States	Yes	Unclear	Unclear	Open-label	ITT	1.0% not entered in adverse event assessment
Benboubker [2014]	Europe, North America, the Asia-Pacific region	Yes	Computer generated	Unclear	Open-label	PP/ITT	0.83% not entered in adverse event assessment

ITT, intention-to-treat; PP, per-protocol; N/A, not available.

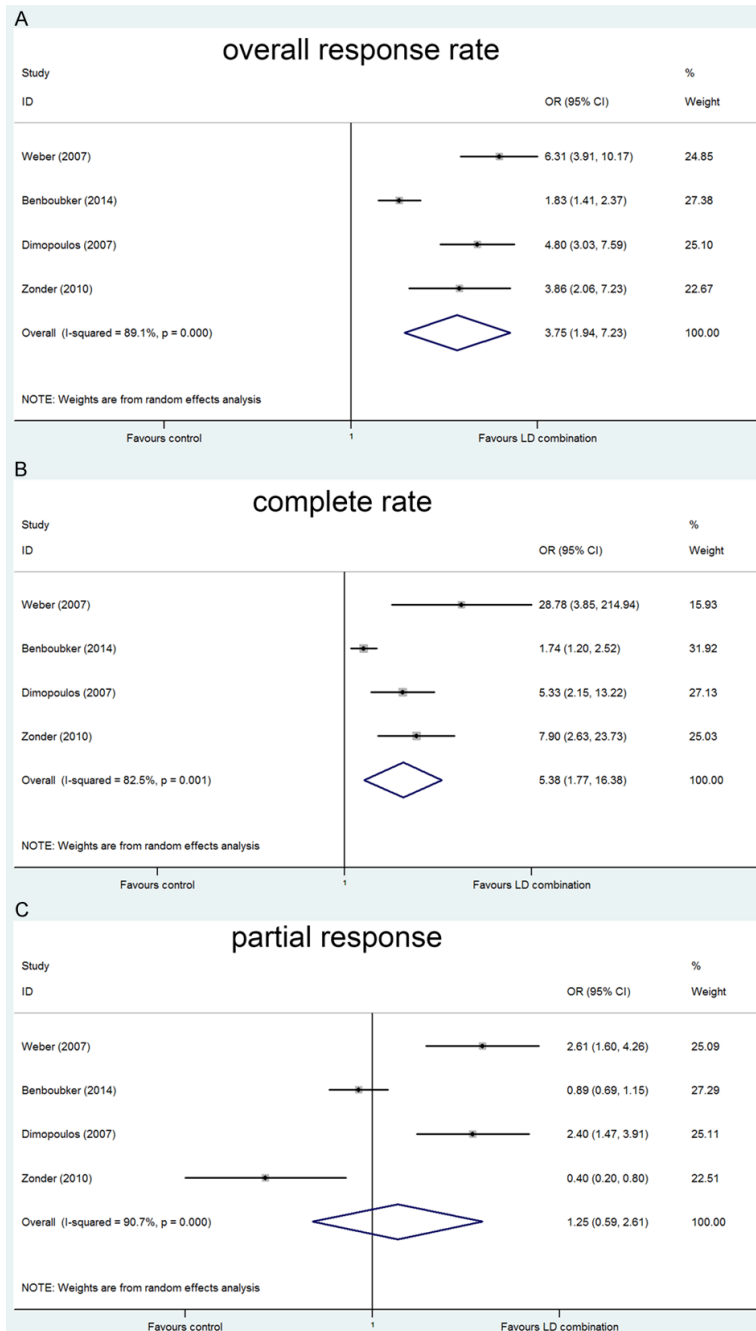


Figure 2. Forest plot displaying the results of the meta-analysis on individual trials and pooled odd ratios for response rates (A) overall response rate (B) complete response (C) partial response (OR = Odds ratio; CI = 95% confidence interval).

ratios (HR) was used for effect sizes of survival data (PFS, OS), and the odd risk (OR) was used for effect of treatment for dichotomous outcomes (CR, ORR, PR of AEs). When each study was identified to have adequate clinical and statistical similarity, data for trials were only

pooled. Forest plots, graphical representations of the analysis, were used to describe the effect estimates for each trial as well as 95% confidence intervals (CIs). In addition, heterogeneity was considered statistically significant when $P < 0.1$ or $I^2 > 50\%$. If significant heterogeneity existed, a randomized effect model was employed to incorporate the variability of data among studies. By contrast, a fixed effect model was employed without obvious heterogeneity. Statistical significance was indicated by $P < 0.05$.

Results

Characteristics of the trials

Our initial search generated 1306 potentially relevant articles, leaving a total of four trials identified in our study [20-23]. Our flowchart for selection of the trials is shown in **Figure 1**. The study results were published between 2007 and 2014, and 1969 patients were enrolled in total. All four trials reported overall response rates, complete rates, progression-free survival, overall survival as well as toxicity. As is shown in **Table 1**, three trials compared LD with placebo plus dexamethasone (PD) treatment, while the other trials compared LD with melphalan-prednisone-thalidomide (MPT) treatment. Control group patients in the trial reported by Zonder et al. [22]

were available to receive crossover therapy upon disease progression. One trial, by Benboubker [23], compared continuous LD versus 18 cycles of LD versus MPT in transplant-ineligible patients with myeloma. Data from the 18 cycles of LD arm was excluded as this con-



Figure 3. Forest plot displaying the results of the meta-analysis on individual trials and pooled hazard ratios for progression-free survival (A) and overall survival (B) in the comparison of LD and PD/MPT regimens (Hazard ratios are presented with 95% confidence intervals).

trol arm could not meet the inclusion criteria that patients continued to accept the assigned drug regimen until disease progression.

Methodological quality of the trials

The methodological quality of the trials is described in **Table 2**. Four trials were multi-center RCTs, of which two trials were double blinded [20, 21] as well as the other two trials were open-labeled [22, 23]. Three studies clearly described an intention-to-treat (ITT) analysis [20-22]. Only one trial reported allocation concealment [20]. Drop-out description was available in two trials [22, 23]. Two trials reported methods of allocation randomization [20, 23].

Response rates

All trials reported response rate with LD therapy. We extracted data from these trials in our analysis. In short, response rate was significantly advanced by the lenalidomide plus dexamethasone regimens in the treatment of patients with myeloma. The weighted OR for ORR (**Figure 2A**) and CR (**Figure 2B**) were 3.75

(95% CI: 1.95 to 7.23) and 5.38 (95% CI: 1.77 to 16.38), respectively, both in favor of LD regimens. There were no statistically significant effects of treatment in the partial response (**Figure 2C**) (OR = 1.25, 95% CI: 0.60 to 2.61). However, there was significant heterogeneity during the trials for complete response ($I^2 = 82.5\%$, $P = 0.001$), overall response rates ($I^2 = 89.1\%$, $P = 0.000$), and partial response ($I^2 = 90.7\%$, $P = 0.000$).

PFS and OS

As initial therapy for MM, Zonder et al. [22] reported that the superiority of lenalidomide plus dexamethasone over the control arm significantly improved one-year PFS (78% vs. 52%, $P = 0.002$) as well as three-year PFS (52% vs. 32%, $P < 0.05$). Meanwhile, this trial also reported that lenalidomide plus dexameth-

asone was associated with no improvement over the overall survival rate compared with the control arm. Dimopoulos et al. [21] reported that the time to progression was significantly improved in the lenalidomide plus dexamethasone group (11.3 vs. 4.7 months with control, $P < 0.001$).

We extracted data obtained from these trials in our analysis [20, 21, 23]. A random-effects statistical model revealed that the pooled HR for PFS (**Figure 3A**) was 0.50 (95% CI: 0.25 to 0.99), in favor of LD. There was evidence of statistically significant heterogeneity between the trials ($I^2 = 94.5\%$, $P = 0.000$). LD regimens showed significant improvement over the control regimens using by a fix-effects statistical model for the analysis of OS (**Figure 3B**) (HR = 0.73, 95% CI: 0.62 to 0.86). There was no significant heterogeneity among the trials ($I^2 = 0$, $P = 0.427$).

Adverse outcomes

As first-line treatment for patients with MM ineligible for transplantation, Benboubker et al.

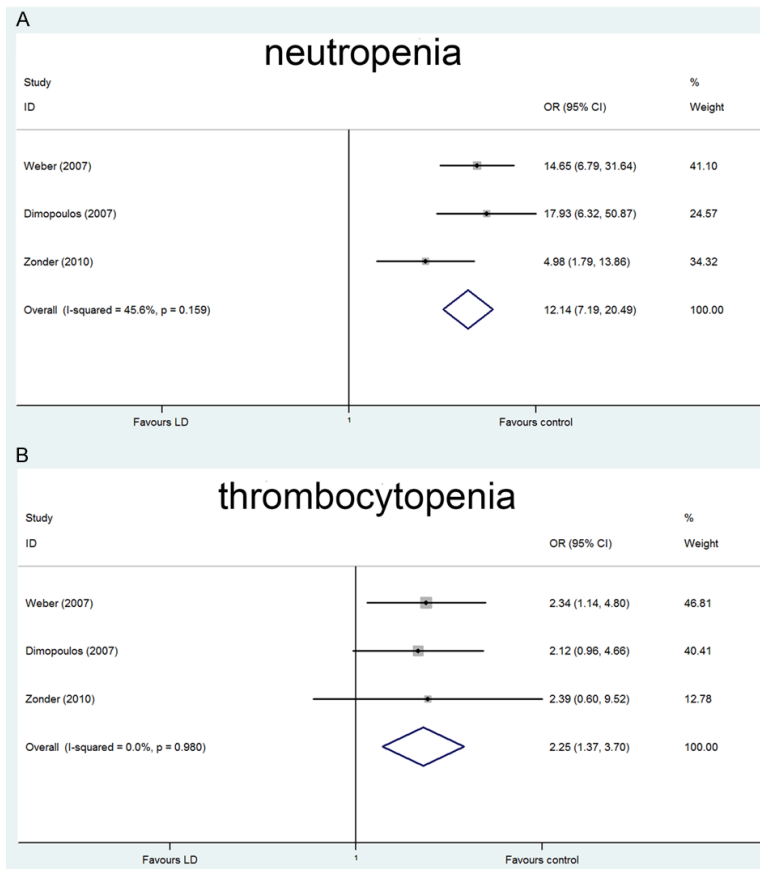


Figure 4. Forest plot displaying the results of the meta-analysis on individual trials and pooled odd ratios for the incidence of grade 3 or higher neutropenia (A) and thrombocytopenia (B) in the comparison of LD and PD/MPT regimens (OR = Odds ratio; CI = 95% confidence interval).

[23] reported that the toxicity of the treatment group, continuous LD and the control arm (MPT). The control arm melphalan-prednisone-thalidomide (MPT) of study design is different from other trials that compared lenalidomide plus dexamethasone with placebo plus dexamethasone treatment. MPT regimen itself also has greater toxic effects than the PD regimen. Therefore, data of adverse outcomes from this trial was excluded.

We analyzed two common adverse effects and found significant differences between the two groups, with more patients in the lenalidomide plus dexamethasone group experiencing neutropenia (OR = 12.14; 95% CI: 7.19 to 20.49), thrombocytopenia (OR = 2.26; 95% CI: 1.37 to 3.70), respectively (**Figure 4A** and **4B**). Some other main adverse events were exhibited in **Table 3**. Lenalidomide plus dexamethasone regimen was associated with an increased risk

of grade 3 or 4 anemia, infection, deep-vein thrombosis and muscle weakness. Our analysis also demonstrated that no significant effects of lenalidomide plus dexamethasone on the incidence of fatigue and dyspnea were observed.

Discussion

Our meta-analysis has revealed that lenalidomide plus dexamethasone had significant clinical activity in patients with MM, including response rate (both overall and complete responses), progression-free survival and overall survival. Several adverse events (i.e., neutropenia, thrombocytopenia, anemia, infection, deep-vein thrombosis and muscle weakness) were more common in the lenalidomide plus dexamethasone group than in the control group.

Recently, preliminary data from early phase I/II trials showed that novel drug combination regimens based

on lenalidomide and dexamethasone induce significantly higher overall objective response rate with lower toxicity, longer time to progression and overall survival compared with thalidomide [15-17, 24]. Lenalidomide can also overcome drug resistance and is well tolerated in patients with relapsed or refractory myeloma [16]. Another promising finding from the included clinical trials [20, 21] showed that the combination therapy is more effective than dexamethasone alone in the treatment without deterioration of pre-existing neuropathy, irrespective of prior thalidomide exposure. Similarly, another study supports this view as well [17]. Given that current therapeutic strategy includes thalidomide and dexamethasone, this finding is encouraging for further research to clarify the clinical activity and novel mechanism of lenalidomide in patients with established resistance to thalidomide treatment. An updated article from Mele et al. [25] retrospec-

Table 3. Main Grade 3 or 4 adverse events

Adverse events	Statistical method	OR (95% CI)	P	I ²
Anemia	Odds ratio (M-H, fixed, 95% CI)	1.746 [1.056, 2.888]	0.030	0.12
Infection	Odds ratio (M-H, fixed, 95% CI)	1.918 [1.332, 2.762]	0	0
Fatigue	Odds ratio (M-H, fixed, 95% CI)	1.526 [0.929, 2.505]	0.095	0
Deep-vein thrombosis	Odds ratio (M-H, fixed, 95% CI)	2.951 [1.667, 5.225]	0	0.43
Muscle weakness	Odds ratio (M-H, fixed, 95% CI)	2.129 [1.107, 4.092]	0.023	0
Dyspnea	Odds ratio (M-H, fixed, 95% CI)	1.158 [0.529, 2.531]	0.714	0

tively studied 290 patients from 12 Italian haematological institutions to evaluate the efficacy and toxicity of this combination as salvage therapy for the treatment of relapsed/refractory MM patients. This retrospective multicenter analysis reported that patients receiving lenalidomide plus dexamethasone have a significantly longer overall survival, time to best response and duration of response. Further research is needed to explore optimal lenalidomide doses and therapeutic strategies individualized in terms of patients' characteristics.

In addition to efficacy, toxicity should also be taken into account. Our study showed that lenalidomide plus dexamethasone increases the incidence of adverse events (i.e., neutropenia, thrombocytopenia, anemia, infection and deep-vein thrombosis). Neutropenia is a common adverse event with lenalidomide therapy. Dose adjustments and/or the administration of granulocyte colony-stimulating factor (G-CSF) are warranted during treatment in patients [20, 21, 26]. Sometimes prophylactic use of G-CSF is recommended in several cases [26]. Similarly, dose adjustments should also be taken into consideration on grade 3-4 thrombocytopenia, if necessary, platelet transfusion can be performed. Infections are at an increased risk as well. Prophylaxis with G-CSF and/or with bacterial antibiotics may be warranted [20, 26]. In our analysis, patients with MM have an increased incidence of grade 3 or 4 thromboembolic events. A recent retrospective study on sixty-two cases confirmed that ambulatory patients with MM who are considered for immunomodulatory drug therapy should be placed on pharmacologic thromboprophylaxis based on individual venous thromboembolism and bleeding risk factors [27]. In addition, alternative ways to prevent venous thromboembolism are needed, such as prophylaxis with either low-molecular weight heparin (LMWH) [22] or

low-dose acetylsalicylic acid when patients receive antiangiogenesis agents. Erythropoietin, associated with the tumor mass, can generally improve with response to treatment. One trial from Weber [20], however, reported that concomitant erythropoietic agents are avoided due to the higher incidence of thromboembolic events in patients. In light of this, we suggest that further studies are needed to balance EPO benefits as well as reduce the risks of occurrence of thromboembolic events in myeloma. Furthermore, a recent study from Rajkumar revealed that low-dose dexamethasone in combination with lenalidomide has lower toxicity than high-dose dexamethasone plus lenalidomide, especially in deep-vein thrombosis and infections [28]. Based on these results, optimized dexamethasone dosage can be manageable when this drug is combined with lenalidomide, at the same time, adequate recognition and management will contribute to improved treatment efficacy on the whole [26].

There were significant heterogeneities with respect to patient population and treatment regimen in some analysis. First, individualized treatment on account of patient characteristics (age, comorbidities), and biological characteristics of the disease, probably affect the outcomes. Second, the dosage and schedule of therapeutic strategies were relatively different across the trials in our analysis. Third, clinical practice in heavily pre-treated patients and clinical factors without uniform standards could have contributed to the heterogeneity.

Besides significant heterogeneities occurred in this review, there are also some limitations. First, the small number of trials met the inclusion criteria. Second, our work was limited based on aggregate study due to lacking adequate individual patient data. Third, our analysis is also limited by the methodological quality of the included trials (**Table 2**). Only two trials

reported an adequate technique for randomized allocation [20, 23] and one trial reported an adequate technique for allocation concealment [20]. Finally, the early unblinded treatment allocation and crossover therapy before study closure included in the Zonder et al, which may also be associated with the statistical power of therapeutic outcomes.

In summary, our findings indicated that treatment with lenalidomide plus dexamethasone significantly improves the response rate, progression-free survival and overall survival. However, several adverse events (neutropenia, thrombocytopenia, anemia, infection and deep-vein thrombosis) are associated with greater incidence with this combination. Therefore, these adverse events should be closely monitored and, if necessary, prophylactic treatment and/or dose adjustments may be administered. This meta-analysis provides a better comprehensive overview of the efficiency and safety of LD regimens in the patients with MM, which helps to further optimize therapeutic strategies individualized for MM patients in the future.

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Disclosure of conflict of interest

None.

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