Efficacy and Safety of Lenalidomide in the Treatment of Multiple Myeloma: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Abstract

Background: Lenalidomide has emerged as an important treatment for patients with multiple myeloma (MM). However, its role in the management of MM is still controversial and requires further clarification. The aim of this study was to evaluate efficacy and safety of lenalidomide for MM using a meta-analysis.

Methods: We searched the electronic databases including: PubMed, EMBASE and the Cochrane Center Register of Controlled Trials. Seven randomized clinical trials were identified, which included a total of 2357 patients with MM who received lenalidomide-containing, noncontaining lenalidomide regimens or placebo as induction therapy or maintenance therapy. The outcomes included overall response (OR) rate, complete response (CR) rate, 3-year progression-free survival (PFS) rate, 3-year overall survival (OS) rate, and different types of treatment-related adverse events. We calculated the risk ratios (*RR*s) as well as their 95% confidence intervals of these outcomes and pooled the results using RevMan 5.2 software.

Results: For patients with previously untreated MM, OR rate and CR rate was significantly higher in lenalidomide-containing group than the control group. For relapsed or refractory MM patients, lenalidomide-containing regimens significantly improved the OR rate, CR rate, 3-year PFS rate and 3-year OS rate. With regard to MM patients after autologous stem cell transplantation, lenalidomide maintenance therapy significantly improved 3-year PFS rate but did not result in improved 3-year OS rate. In terms of toxicities, lenalidomide therapy has a higher rate of Grade 3–4 grade cytopenias, infection, deep-vein thrombosis, and diarrhea. Furthermore, the incidence of second primary malignancies was significantly higher in the lenalidomide group.

Conclusions: The lenalidomide-containing regimens as induction therapy clearly increased response rates and improved intervals of survival with acceptable toxicity rates for patients with MM. However, when physicians choose to use the lenalidomide as maintenance therapy, whether the benefits outweigh the risks should be taken into account.

Key words: Lenalidomide; Meta-analysis; Multiple Myeloma

Introduction

Multiple myeloma (MM) is the second most common hematologic neoplasm that is characterized by a malignant expansion of monoclonal plasma cells in the bone marrow often accompanied with osteolytic lesions, renal failure, anemia, and hypercalcemia.[1] Although MM currently remains an incurable malignancy, with the introduction of high-dose chemotherapy, followed by autologous stem cell transplantation (ASCT) and several novel agents (thalidomide, lenalidomide, and the proteasome inhibitor bortezomib), considerable progress has been made in the outcomes of patients with MM.[2-5] These novel therapies have produced higher response rates and improved intervals of survival. Because of thalidomide's serious toxicity and limited efficacy, it has been gradually replaced by lenalidomide.

Lenalidomide (Revlimid, Celgene, Switzerland), an analogue of thalidomide, is a kind of the immunomodulatory drug with potent anti-angiogenic and anti-inflammatory properties.[6] The mechanisms underlying anti-MM effect of lenalidomide has been identified by several studies,[7-10] including induction of apoptosis, decreased production of cytokines (interleukin-6, tumor necrosis factor-α, vascular endothelial growth factor), inhibition of angiogenesis, blocked binding of MM cells to the bone marrow stromal cells and stimulating host natural killer cell anti-MM

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.156134

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immunity. Lenalidomide-containing therapy has been shown to improve the outcomes of patients with newly diagnosed or previously treated MM.[11-16] In addition, lenalidomide maintenance therapy, significantly improve the progression-free survival (PFS) of both young patients after ASCT and old patients after conventional induction chemotherapy, but the effect on overall survival (OS) was controversial.[12,17,18] In addition, lenalidomide has been shown to further increase the risk of adverse events (AEs), especially when combined with glucocorticoids and/or cytotoxic drugs.[12,15,16,19,20]

Therefore, we conducted a systematic meta-analysis in order to assess the efficacy and safety of lenalidomide in the treatment of patients with MM and specifically to elucidate whether lenalidomide-containing regimens offer a survival advantage over nonlenalidomide-containing regimens.

Methods

Search stratery

Electronic databases including PubMed, EMBASE and the Cochrane Center Register of Controlled Trials were searched using the following search terms: "Randomized," "myeloma" and "lenalidomide." Other potentially eligible studies were also manually searched according to the reference lists from the trials identified. All the data retrieved were updated to May 2013.

Selection of studies and data extraction

Clinical trials were selected if they met the following criteria: (1) Study design: Prospective randomized controlled trial (RCT); (2) study object: Patients with newly diagnosed or previously treated MM; (3) acceptable comparisons: Lenalidomide-containing regimens versus nonlenalidomide-containing regimens for newly diagnosed or relapsed/refractory MM treated with standard chemotherapy (other drugs of these regimens must be the same), or lenalidomide maintenance therapy versus placebo for MM after ASCT; and (4) the study recorded the necessary data about therapy efficacy and safety. To avoid publication bias, we included trials regardless of publication status and language. When more than one of the same or overlapping publications was reported in several studies, only the most complete data were used for further combined analysis.

The following data were extracted from each eligible study: The name of the first author, year of publication, study design, patient details, intervention received, number of subjects, age, overall response (OR), complete response (CR), PFS, OS, and Grade 3 or 4 toxicities associated with lenalidomide treatment (neutropenia, febrile neutropenia, anemia, thrombocytopenia, infection, fatigue, nausea, diarrhea constipation, deep-vein thrombosis (DVT) and second primary malignancies [SPMs]). When the data required for the analysis could not be extracted, attempts were made to contact the investigators who conducted the studies.

Outcome measures

Outcomes assessed by this meta-analysis included OR, CR, 3-year OS, 3-year PFS and different types of treatment-related AEs. OS was defined as the time from the date of randomization to death from any cause. PFS was defined as the time from the date of randomization until disease progression or death. As for AEs, we analyzed Grade 3 or 4 hematological and nonhematological toxicity, as well as SPMs.

Responses to treatment and disease status were assessed with the use the European Group for Blood and Marrow Transplantation criteria,[21] and a very good partial response (VGPR) was defined according to the International Uniform Response Criteria for Multiple Myeloma.[22] National Cancer Institute Common Toxicity Criteria was used to assess AEs.[23]

Quality assessment

To avoid bias in the data abstraction process, the two hematologist investigators (Shu-Kai Qiao and Han-Yun Ren) independently abstracted the data from all identified trails and subsequently screened search results. All data were checked for internal consistency, and disagreements were resolved by discussion. Methodological quality of each clinical trial was evaluated using the modified Jadad quality scores,[24] including the presence of randomization, allocation concealment, blinding, and withdrawal/dropout. A general quality score was assigned to each study as follows: Non-RCTs (0), low quality studies (1–3), and high quality studies (4–7).

Statistical analysis

Statistical analyses were performed using Review Manager 5.2 statistical software (Cochrane Collaboration, Denmark). Dichotomous data were expressed as risk ratio (*RR*) and 95% confidence intervals (*CI*s). We assessed the heterogeneity in the results of the trials using Cochrane Q statistic and the I^2 value. If a $P < 0.10$ or $I^2 > 50\%$, the assumption of homogeneity was deemed invalid and the Mantel–Haenszel random-effects model was used after exploring the causes of heterogeneity. Otherwise, we conducted a meta-analysis using a fixed-effect model. We defined a $P < 0.05$ as statistically significant for all outcomes.

Results

Search results

The search strategy identified 993 potentially relevant studies, of which 965 were excluded after screening titles and abstracts. Full text or further details were retrieved for the remaining 28 studies. Of those, 8 non-RCT studies, 5 duplicate data, 5 control not suitable studies, and 3 other inclusion criteria not met studies were excluded. Eventually, seven RCTs that included 2357 patients were identified for the meta-analysis.[12,15-18,25,26] Figure 1 shows the studies selection process. The k statistic for the agreement between the two reviewers for study selection was excellent ($K = 0.78$). The basic characteristics and quality scores of included studies were listed in Table 1.

Table 1: Characteristics of included studies in the meta-analysis

Study, year	Study design	Patient details	Intervention	Number of patients	Ages (years)	Outcomes	Jadad score
Dimopoulos *et al.* 2007	RCT	Relapsed or refractory	Experiment: L-DEX	176	63 (33–84)	OS, PFS, AEs	5
			Control: P-DEX	175	64 (40–82)		
Weber *et al.* 2007	RCT	Relapsed	Experiment: L-DEX	177	64 (36–86)	OS, PFS, AEs	6
			Control: P-DEX	176	62 (37–85)		
Zonder *et al.* 2010	RCT	Newly diagnosed	Experiment: R-DEX	97	48	OS, PFS, AEs	6
			Control: P-DEX	95	45		
Kumar *et al.* 2012	RCT	Previously untreated	Experiment: VDCR	48	61.5 (41–81)	OS, PFS, AEs	5
			Control: VDC	33	62 (40–75)		
Palumbo *et al.* 2012	RCT	Newly diagnosed	Experiment: MPR + R	152	71 (65–87)	OS, PFS, AEs	6
			Control: MP + P	154	72 (65–91)		
Attal *et al.* 2012	RCT	ASCT	Experiment: L	307	55 (22–67)	OS, PFS, AEs	6
			Control: P	307	55 (32–66)		
McCarthy *et al.* 2012	RCT	ASCT	Experiment: L	231	59 (29–71)	OS, PFS, AEs	6
			Control: P	229	58 (40–71)		

RCT: Randomized clinical trial; ASCT: Autologous stem cell transplantation; OS: Overall survival; PFS: Progression-free survival; AEs: Adverse events.

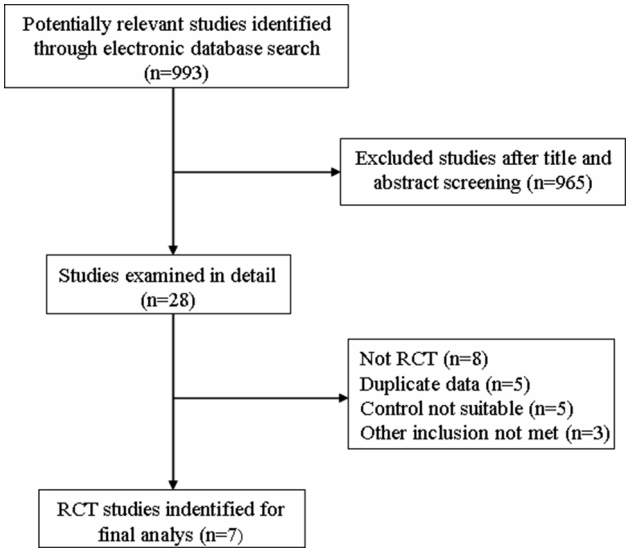

Figure 1: Study selection for meta-analysis. RCTs: randomized clinical trials.

Three RCTs reported the results of the patients with previously untreated MM,[12,25,26] two RCTs reported the results of patients with refractory or relapsed MM,[15,16] the other two RCTs reported the results of lenalidomide maintenance therapy in MM patients after ASCT.[17,18]

Previous untreated multiple myeloma

Three RCTs, with a total of 544 patients, suggested that lenalidomide-containing regimens achieved a statistically significant higher OR rates (pooled *RR*: 1.49; 95% *CI*: 1.30–1.71; $P < 0.00001$, incidence, 75.5% vs. 50.6%, Figure 2a) and CR rates (pooled *RR*: 4.08; 95% *CI*: 2.02–8.23; $P < 0.0001$, incidence, 13.4% vs. 3.4%; Figure 2b) compared with the no lenalidomide-containing regimens. There was no significant heterogeneity among the reported OR ($P_{heterogeneity} = 0.16$; $I^2 = 46\%$) and CR ($P_{heterogeneity} = 0.38$; $I^2 = 0\%$). Considering the differences in consolidation/maintenance therapy after initial induction therapy and follow-up time, we did not perform meta-analyses for PFS and OS for previous untreated MM.

Relapsed or refractory multiple myeloma

Two RCTs reported the data of a total of 704 patients with relapsed or refractory MM, who had received at least one previous antimyeloma treatment. Lenalidomide-containing regimens achieved a statistically significant higher OR rates (pooled *RR*: 2.76; 95% *CI*: 2.23–3.42; $P < 0.00001$; incidence, 60.6% vs. 21.9%; Figure 3a) and CR rates (pooled *RR*: 8.61; 95% *CI*: 1.59–46.60; $P = 0.01$; incidence, 15.0% vs. 2.0%; Figure 3b) compared with the no lenalidomide-containing group. There was no significant heterogeneity among the reported OR ($P_{heterogeneity} = 0.36$; $I^2 = 0\%$), but heterogeneity was found with respect to the reported CR ($P_{heterogeneity} = 0.11$; $I^2 = 62\%$), and hence the random-effects model was used. In terms of PFS and OS, patients treated with the lenalidomide-containing regimens had significantly longer 3-year PFS (pooled *RR*: 1.48; 95% *CI*: 1.24–1.75; $P < 0.00001$; Figure 4) and 3-year OS (pooled *RR*: 1.12; 95% *CI*: 1.01–1.24; $P = 0.03$; Figure 5) than no lenalidomide-containing regimens. There was no significant heterogeneity between the reported 3-year PFS ($P_{heterogeneity} = 0.90$; $I^2 = 0\%$) and 3-year OS ($P_{heterogeneity} = 0.92$; $I^2 = 0\%$), and the fixed effects model was used.

Maintenance therapy for multiple myeloma postautologous stem cell transplantation

Two RCTs reported the data of a total of 1074 patients with MM after ASCT, who received lenalidomide or placebo as maintenance therapy. We did not perform meta-analyses for OR and CR in MM patients post-ASCT because the relevant data could not be obtained from the study by McCarthy *et al*.[17] Lenalidomide maintenance therapy significantly improved 3-year PFS (pooled *RR*: 1.43; 95%

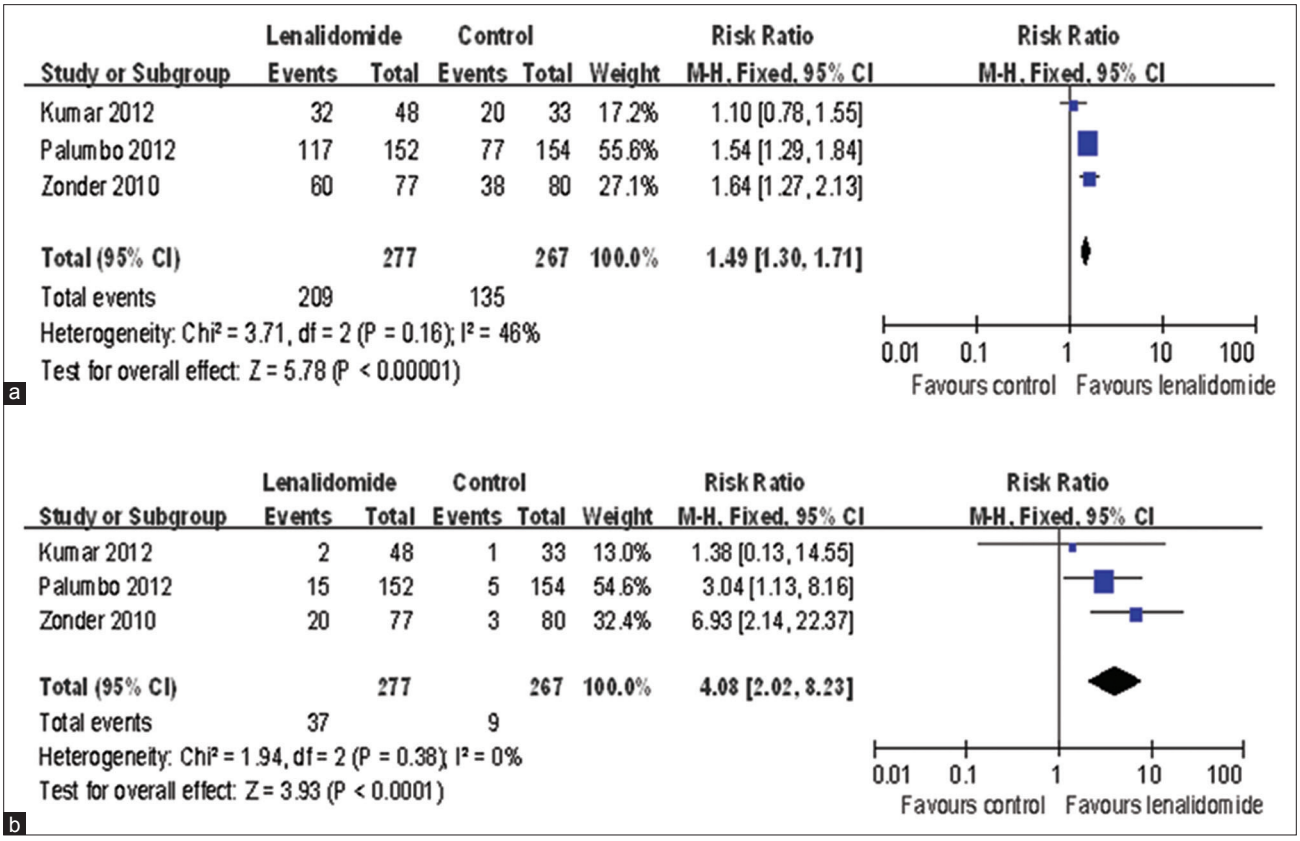

Figure 2: Forest plot of response rates comparing lenalidomide with control for previous untreated multiple myeloma. (a) Overall response; (b) Complete response.

CI: 1.28–1.60; $P < 0.00001$; $P_{heterogeneity} = 0.43$; $I^2 = 0\%$; Figure 6) among patients post-ASCT, but not significantly improved OS (pooled *RR*: 1.02; 95% *CI*: 0.89–1.18; $P = 0.75$; $P_{heterogeneity} = 0.01$; $I^2 = 84\%$; Figure 7). There was a significant heterogeneity with respect to the reported OS rate, so the random-effects model was used.

Toxicities

The data of major AEs were extracted from the seven RCTs and analyzed by a meta-analysis. As for hematological AEs, patients treated with lenalidomide had a significantly higher rate of Grade 3–4 neutropenia, febrile neutropenia, anemia, and thrombocytopenia. Of those, neutropenia was the most common (48.9% vs. 14.7%; $P < 0.00001$), followed by thrombocytopenia (17.4% vs. 7.4%; $P < 0.00001$). The results of major hematological AEs were described in Table 2. With regard to nonhematological AEs, lenalidomide treatment was associated with a significantly higher rate of grade 3/4 infection, DVT and diarrhea. Of those, infection is the most common (14.3% vs. 7.7%; $P < 0.0001$), followed by DVT (6.2% vs. 2.3%; $P = 0.0001$). The results of major nonhematological AEs were listed in Table 3. Also, three trials[8,13,14] and a second analysis of two trials[15,16] by Dimopoulos *et al*.[27] reported data on SPMs. There were 75 and 25 SPMs, respectively, observed in a sample of 1042 patients with lenalidomide therapy and 1035 patients with placebo. Lenalidomide therapy had a significantly higher risk of SPMs (pooled *RR*: 2.92; 95% *CI*: 1.87–4.56; $P < 0.00001$; incidence, 7.2% vs. 2.4%; Figure 8). Heterogeneity was found for some AEs, which was possibly because of the use of different agents at various dosages in these studies.

Discussion

Although the treatment of MM had undergone significant development during the past decades, MM was still difficult to cure and require a long-term disease control. Some clinical trials showed that the most of MM patients often had a good respond to initial standard therapy, but the disease ultimately recurred and became refractory to further treatment over the course of time. Richardson *et al*. first reported a phase I clinical study of lenalidomide in relapsed and refractory MM, 71% patients (90% *CI*: 52–85%) demonstrated benefit from treatment, suggesting significant anti-MM activity of lenalidomide.[7] Subsequently, a multicenter randomized phase II study evaluated 2 dose regimens of lenalidomide (30 mg once-daily or 15 mg twice-daily oral) for relapsed and refractory MM.[14] OR rate to lenalidomide alone was 25% (24% for once-daily and 29% for twice-daily). Recently, two multicenter, double-blind, phase III RCTs (MM009 and MM010) also observed both the safety and efficacy of lenalidomide in the relapse or refractory setting.[15,16] The results showed that patients with lenalidomide plus dexamethasone therapy, who achieved a

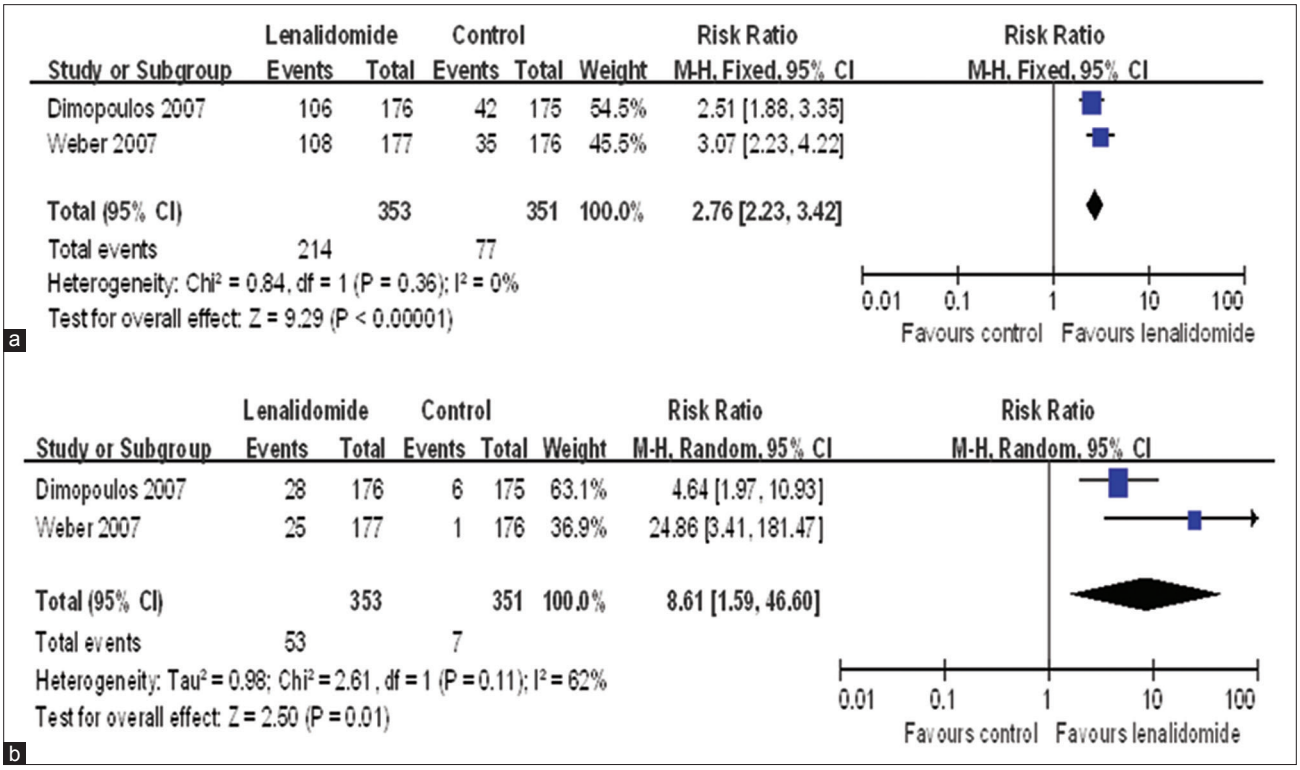

Figure 3: Forest plots of responses rate comparing lenalidomide with control for relapsed or refractory multiple myeloma. (a) Overall response; (b) Complete response.

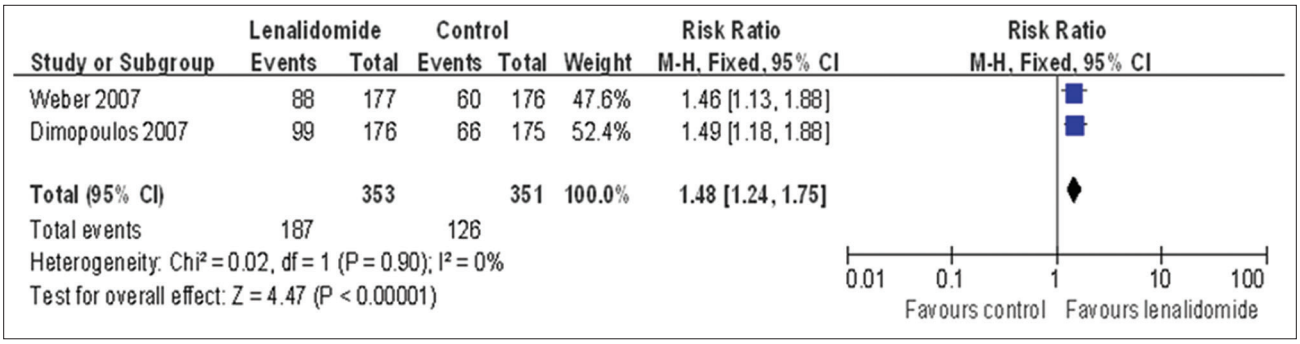

Figure 4: Forest plot of 3-year progression-free survival rate comparing lenalidomide with control for relapsed or refractory multiple myeloma.

Figure 5: Forest plot of 3-year overall survival rate comparing lenalidomide with control for relapsed or refractory multiple myeloma.

CR or VGPR, had a significantly longer PFS and OS than those in whom treatment resulted in only a PR. Therefore, the aim of induction therapy was as quickly as possible to the achievement of the deepest response.

The results of this meta-analysis demonstrated that lenalidomide-containing regimens used as induction therapy in previously treated MM patients had produced a significant improvement in terms of both response

rates and the intervals of survival. Similar to the former, lenalidomide-based regimens for relapsed or refractory MM patients also significantly increased the OR and CR rate. Importantly, lenalidomide was associated with better 3-year PFS rate (53.0% vs. 35.9%; $P < 0.00001$) and 3-year OS rate (72.8% vs. 65.0%; $P = 0.03$).

Despite the positive results with lenalidomide maintenance therapy has been reported in the post-ASCT setting, many open questions remain. These included the optimal dose, schedule, and duration of therapy as well as the treatment-related toxicities. In addition, whether all patients or only those with a suboptimal response to ASCT should receive lenalidomide maintenance after ASCT needed to clarify. Our pooled data suggested that lenalidomide maintenance therapy in MM patients after ASCT significantly prolonged 3-year PFS (65.2% vs. 45.5%; $P < 0.00001$), but did not improve 3-year OS (82.2% vs. 81.0%; $P = 0.75$) when compared with placebo control. PFS could be useful as a valid regulatory end point when evaluating a new drug for the treatment of MM, because it was a reasonable marker of clinical benefit. However, a statistically significant improvement of OS was still essential to the assessment of lenalidomide maintenance therapy. In fact, our pooled data did not demonstrate a convincing and meaningful increase of OS and no clear evidence supports a benefit of maintenance therapy for patients after ASCT. Currently, lenalidomide maintenance therapy could not be advised for MM patients in

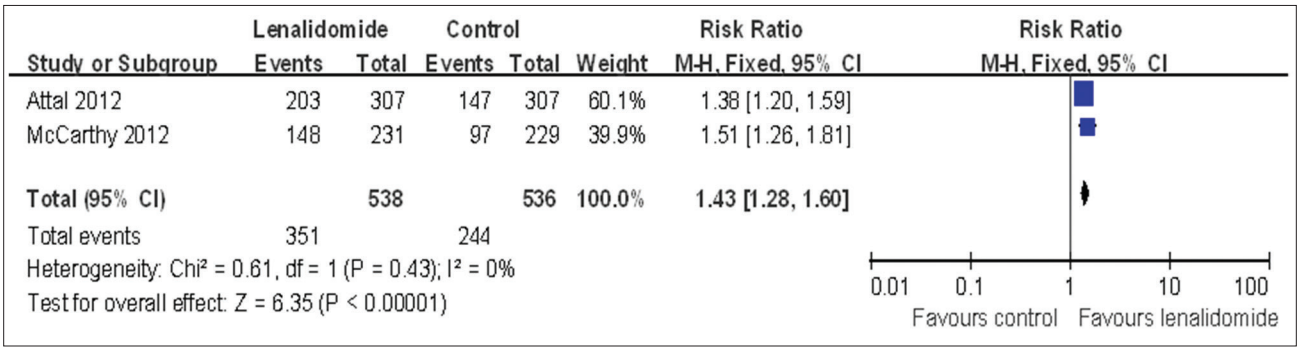

Figure 6: Forest plot of 3-year progression-free survival rate in the randomized controlled trials comparing lenalidomide with placebo as maintenance therapy for multiple myeloma after autologous stem cell transplantation.

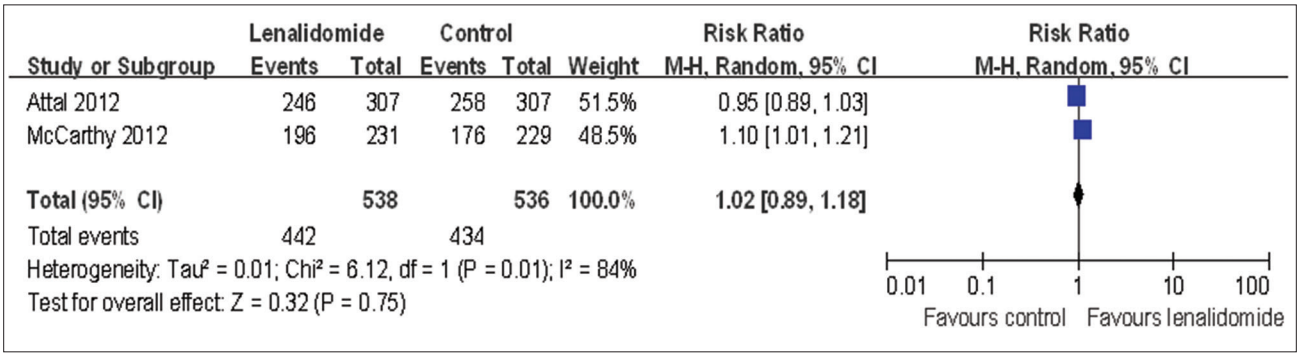

Figure 7: Forest plot of 3-year overall survival rate in the randomized controlled trials comparing lenalidomide with placebo as maintenance therapy for multiple myeloma after autologous stem cell transplantation.

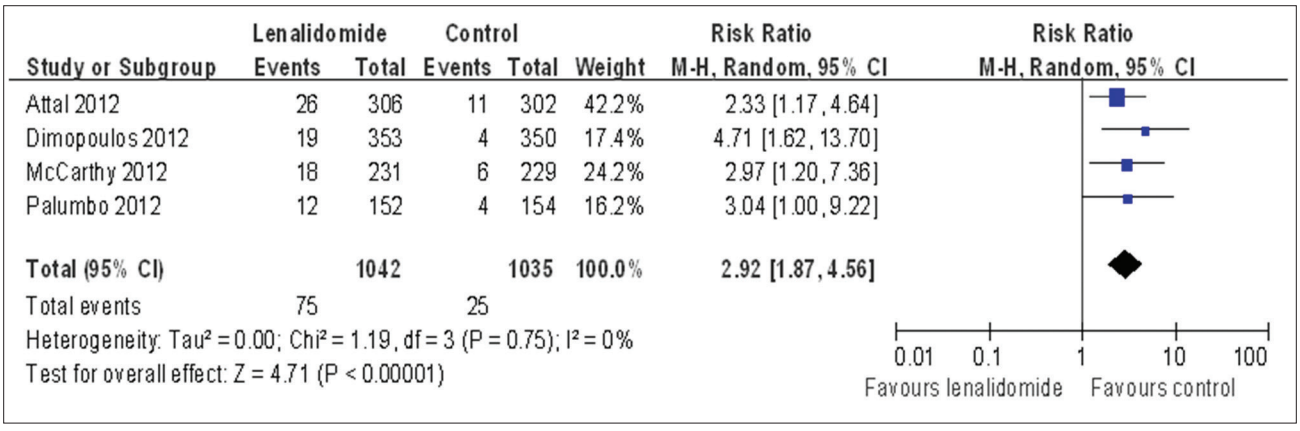

Figure 8: Forest plot of risk ratio on second primary malignancies in the randomized controlled trials comparing lenalidomide with control.

Table 2: Summary of grade 3–4 hematological AEs related to lenalidomide therapy

Hematological AEs	Number of patients with available data	R-arm *n*/%	C-arm *n*/%	Exact *RR* (95% *CI*)	*P*	*P* for homogeneity
Neutropenia	2348	580/48.9	171/14.7	3.49 (2.45–4.99)	0.00001	0.0001
Febrile neutropenia	2158	43/3.9	6/0.6	5.54 (2.61–11.76)	<0.00001	0.47
Anemia	2348	113/9.5	57/4.9	1.95 (1.45–2.64)	<0.0001	0.43
Thrombocytopenia	2348	206/17.4	86/7.4	2.35 (1.86–2.97)	<0.00001	0.65

R-arm: Lenalidomide-containing therapy arm; C-arm: Control arm; AEs: Adverse events; *CI*: Confidence interval; *RR*: Risk ratio.

Table 3: Summary of grade 3–4 nonhematological AEs related to lenalidomide therapy

Nonhematological AEs	Number of patients with available data	R-arm *n*/%	C-arm *n*/%	Exact *RR* (95% *CI*)	*P*	*P* for homogeneity
Infection	1807	130/14.3	69/7.7	1.87 (1.42–2.46)	<0.0001	0.59
DVT	1807	56/6.2	21/2.3	2.63 (1.42–2.46)	0.0001	0.52
Fatigue	2348	216/18.2	48/4.1	2.67 (0.98–7.30)	0.06	<0.00001
Nausea	1392	8/1.1	2/0.3	2.97 (0.81–10.89)	0.10	0.92
Diarrhea	2348	39/3.3	6/0.9	3.41 (1.78–6.54)	0.0002	0.67
Constipation	1392	10/1.4	2/0.3	3.63 (1.02–12.97)	0.05	0.46

DVT: Deep-vein thrombosis; R-arm: Lenalidomide-containing therapy arm; C-arm: Control arm; AEs: Adverse events; *CI*: Confidence interval; *RR*: Risk ratio.

post-ASCT setting, unless conclusive evidence to ascertain a survival advantage. Maintenance therapy only might be recommended in patients who had unfavorable cytogenetic abnormalities or a high risk gene expression profile.

With regards to toxicities, previous studies reported that lenalidomide therapy was quite well tolerated for most of the MM patients.[11,12,14] Cytopenias, infection, fatigue, and other some common adverse effects were rather easily controlled. Unlike thalidomide, single-agent lenalidomide was rarely associated with an increased risk of peripheral neuropathy and DVT,[7] but lenalidomide combined with dexamethasone had been associated with an increased risk of DVT.[15,16] Lenalidomide was a complex immunomodulatory drug, whether other serious adverse effects would be recognized only with long-term use. Our pooled results indicated that cytopenias were the most frequent manifestation of hematological toxicities after lenalidomide therapy. Grade 3–4 neutropenia, thrombocytopenia, anemia and febrile neutropenia were significantly higher in lenalidomide therapy group than control group, but the incidence of anemia and febrile neutropenia was relatively low, only 9.5% and 3.9%, respectively. In terms of nonhematological toxicities, lenalidomide therapy produced a higher rate of Grade 3–4 infection, DVT and diarrhea, but the incidences of Grade 3–4 fatigue, nausea and constipation were not significantly increased. Although our results showed an increased risk of DVT (6.2% vs. 2.3%; $P = 0.0001$) after lenalidomide-containing regimens therapy, statistically significant difference disappeared if excluded the studies of lenalidomide in combination with dexamethasone (2.0% vs. 0.8%; $P = 0.18$). In addition, patients with lenalidomide therapy had a significantly higher risk of SPMs (7.2% vs. 2.4%; $P < 0.00001$) compared with placebo control.

There were some limitations to this meta-analysis. First, the major problem was that the characteristics of patient population varied across studies in terms of duration of treatment, dosages, and the follow-up, resulting in heterogeneity. Second, our analysis was limited to the available published data, which may lead to the possibility of omission unpublished or ongoing trials at the time of the writing of this paper. Third, formal test of publication bias was not conducted because of a relatively small number of RCTs included. Finally, the differences in consolidation/maintenance therapy after induction therapy or post-ASCT might attribute to a potential heterogeneity of PFS and OS. These defects may reduce the credibility of the results to some extent, and increased the numbers of trials with larger sample sizes will be necessary to confirm our findings in future studies.

Conclusion

This meta-analysis demonstrates that lenalidomide-containing regimens were associated with better response rates and survival rates with acceptable toxicity rates for the induction treatment of MM. However, lenalidomide maintenance therapy does not improve OS at the price of the increased AEs. Continued studies are needed to ascertain whether lenalidomide maintenance therapy is beneficial to MM patients after ASCT.

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Received: 20-01-2015 **Edited by:** Yi Cui
How to cite this article: Qiao SK, Guo XN, Ren JH, Ren HY. Efficacy and Safety of Lenalidomide in the Treatment of Multiple Myeloma: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Chin Med J 2015;128:1215-22.
Source of Support: Nil. **Conflict of Interest:** None declared.