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Original Article

Lenalidomide after stem-cell transplantation for multiple myeloma: a meta-analysis of randomized controlled trials

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Abstract: The efficacy and safety of lenalidomide maintenance therapy after ASCT in patients with MM has been in question. In order to address the issue, we conducted a meta-analysis of two randomized double-blind placebo-controlled studies encompassing 1074 patients treated with lenalidomide or placebo maintenance therapy after ASCT. The predominant clinical outcomes of interest were overall survival (OS), progression-free survival (PFS), and adverse events. There was a marked benefit in PFS with lenalidomide (Odds Ratio [OR] = 2.5, 95% confidence interval [CI] = 1.93 to 3.24). There was statistically non-significant tendency toward benefit in OS with lenalidomide (OR = 1.21, 95% CI = 0.65 to 2.24). For adverse events, more patients in lenalidomide treatment arm experienced neutropenia (OR = 4.88, 95% CI = 3.67 to 6.50), infection (OR = 2.82, 95% CI = 1.67 to 4.73), hematologic cancers (OR = 3.31, 95% CI = 1.30 to 8.41), and solid tumors (OR = 2.24, 95% CI = 1.01 to 4.98). No significant differences were seen with deep vein thrombosis (OR = 2.15, 95% CI = 0.92 to 5.06), peripheral neuropathy (OR = 1.50, 95% CI = 0.53 to 4.25), thrombocytopenia (OR = 1.05, 95% CI = 0.12 to 9.54), and anemia (OR = 1.36, 95% CI = 0.02 to 83.86). Based on these results, we conclude that lenalidomide maintenance therapy for patients with MM after ASCT was effective in the improvement of PFS. However, treatment-related adverse events must be close monitored. Although there was a trend for increased OS with lenalidomide, there was no statistically significant difference in OS between lenalidomide maintenance therapy arm and placebo maintenance therapy arm. Therefore, longer follow-up and additional high quality RCTs were needed to evaluate the effects of lenalidomide maintenance on OS.

Keywords: Lenalidomide, multiple myeloma, maintenance therapy, meta-analysis

Introduction

Multiple myeloma (MM) is an incurable disease characterized by the accumulation of clonal plasma cells in the bone marrow [1]. It is the second most common hematological malignancy, and accounts for about 1% of all new cancer incidence and mortality [2, 3]. High-dose chemotherapy with autologous stem-cell transplantation (ASCT) is a standard frontline treatment for MM [4]. Unfortunately, most patients with MM relapse or exhibit disease progression after transplantation. Therefore, maintenance therapies have been added in attempt to improve overall survival (OS) [5]. Traditional chemotherapy (eg. low-dose melphalan), interferon, and prednisone have been used for maintenance therapy, but their long-term use is limited by marked toxicity and modest efficacy [6]. Thalidomide maintenance therapy has been shown to be effective at improving progression-free survival (PFS) [7-11]. However, long-term thalidomide use is plagued by severe neuropathy and does not improve OS in patients who achieved a complete response or a very good partial response or who had chromosome 13 deletion. Thalidomide maintenance therapy may even be detrimental in patients with high-risk cytogenetics [6]. The oral, immunomodulatory drug lenalidomide is a newer alternative for effective post-transplantation maintenance therapy. Lenalidomide has shown promise in patients with MM and is an appealing agent for long-term use because of its activity at doses

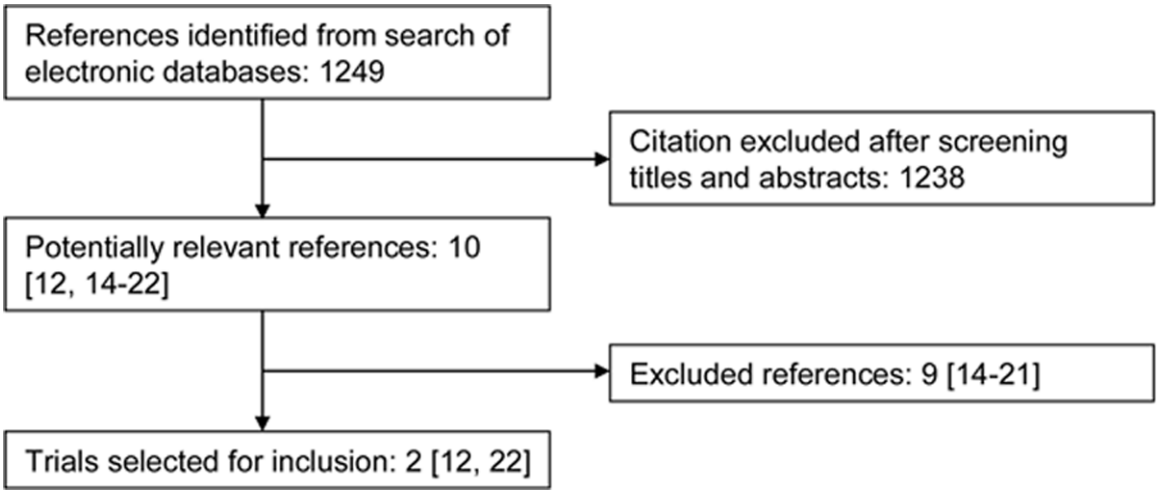

Figure 1. Flowchart of the selection of studies.

lower than induction and its favorable toxicity profile [12, 13].

Yang B et al [14]. performed a meta-analysis examining the efficacy and safety of lenalidomide for MM, using seven trials. Their meta-analysis demonstrated that lenalidomide therapy increased PFS in patients with newly diagnosed MM, but didn't significantly improve OS. Notably, lenalidomide doses and treatment regimens differed between trials in this meta-analysis. Perhaps a deeper problem, though, was that the types of MM patients were different, including those ineligible for transplantation, with untreated symptomatic MM, with newly diagnosed, relapsed or refractory MM, nonprogressive MM after transplantation, etc. Furthermore, subgroup analyses to examine the efficacy and safety of lenalidomide on these different MM patients were not performed. These factors may have contributed to the marked heterogeneity in most of their outcomes. Therefore, it has remained unclear whether lenalidomide maintenance therapy prolongs the time to disease progression and improves OS after ASCT in patients with MM. To this end, herein we report our attempt to clarify the relative benefits and risks of lenalidomide maintenance therapy after ASCT in MM patients. We reviewed the literature to identify randomized controlled trials (RCTs) that examined lenalidomide maintenance therapy after ASCT in patients with MM and identified two [12, 22]. We then performed a combined analysis of these trials in an attempt to clarify the relative benefits and risks of lenalidomide maintenance therapy after ASCT in patients with MM.

Methods

Search strategy

We used PubMed, the Cochrane Library, the ClinicalTrials.gov registry, and conference proceedings from each of the American Society of Hematology, the American Society of Clinical Oncology, and European Hematology Association to locate all relevant studies published up to March 2014. Search terms included "lenalidomide or revlimid" and "myeloma", with 'the related articles' function in PubMed to identify other potentially relevant articles. All the references of retrieved articles were also evaluated. Data was collected only from published, peer-reviewed papers.

Selection criteria

Only phase 3 RCTs that compared lenalidomide maintenance therapy with placebo maintenance therapy after ASCT for patients with MM were included. The treatment strategy and the criteria used for selecting patients needed to be reported, as did clinical outcomes or safety of the treatments. The eligibility of each study was assessed independently by two investigators.

Data extraction and methodological quality assessment

The quality of trials was evaluated by two independent reviewers by examining the adequacy

Table 1. Characteristics of studies fulfilling inclusion criteria in the meta-analysis

Author [Year]	Inclusion criteria	No. of patients (% of male)	Age, mean (range)	Intervention
Attal [2012]	< 65 years No progression after first-line ASCT	L:307 (55) P:307 (59)	L:55 (22-67) P:55 (32-66)	Consolidation (L: 25 mg/d, d1-21, every 28 d cycle, 2 cycles) Maintenance (L: 10 mg/d for the first 3 months, increased to 15 mg if tolerated)
McCarthy [2012]	18-70 years No progression in the first 100 days After ASCT	L:231 (52.4) P:229 (56.3)	L:59 (29-71) P:58 (40-71)	L: 10 mg/d, 100 d after transplantation

L: lenalidomide; P: placebo; ASCT: autologous stem-cell transplantation; d: day.

Table 2. Methodological quality assessment of included trial

Author [Year]	Location	Allocation generation	Allocation concealment	Double blinding	Data analysis	Drop-out	Power analysis	Other risk of bias
Attal [2012]	France, Belgium, Switzerland	Unclear	Unclear	Double blinded	ITT	7.0%	Yes	An increased incidence of second primary make lenalidomide unable to maintain a long time
McCarthy [2012]	United States	Unclear	Unclear	Double blinded	ITT	N/A	Yes	Patients in the placebo arm could cross over to lenalidomide arm

ITT: intention-to-treat; N/A: not available.

of the allocation generation, allocation concealment, double blinding, data analysis, dropouts, power analysis and other risk of bias. Two reviewers performed data extraction independently based on selection criteria. If a disagreement arose, agreement was achieved through consultation with a third reviewer.

Statistical analysis

For each trial, the effect of lenalidomide maintenance treatment was expressed as overall response (OR) with 95% CI. Both the fixed effects model and random effects model were used to calculate the pooled OR. Heterogeneity was assessed by the Cochrane Q test. Statistically significant heterogeneity was considered as $P < 0.05$ or I^2 statistic > 50%. The random effects model was selected when heterogeneity was significant. The publication bias was determined by funnel plot. Revman software (5.2) was used to perform all calculations.

Results

Literature search results

Our initial search identified 1249 references, of which 10 trials were considered potentially relevant by title and abstract. Among them, two papers were excluded because lenalidomide was used as salvage treatment [15, 16]. Two studies were excluded because patients with MM didn't receive ASCT before lenalidomide maintenance treatment [17-19]. One was excluded because it included donor-lymphocyte infusion treatment [20]. Others were excluded because patients with MM received nonmyeloablative allogeneic stem cell transplantation instead of ASCT before lenalidomide maintenance treatment [21] or a comparison of lenalidomide maintenance therapy with placebo maintenance therapy was not done [22]. In total, two trials [12, 23], including 1074 patients, fulfilled the criteria for this meta-analysis (**Figure 1**).

Description of included trials

An outline of the two trials was provided in **Table 1**, and their methodological quality was summarized in **Table 2**. Both trials were published in 2012. Both reported the efficacy and safety of lenalidomide maintenance therapy after ASCT in patients with MM, double blinding of the participants and outcome assessors, used intention-to-treat analysis, and described power analysis. Only Attal et al. Reported the number of dropouts (7%), which was acceptable. Neither trial described the methods of allocation generation and allocation concealment.

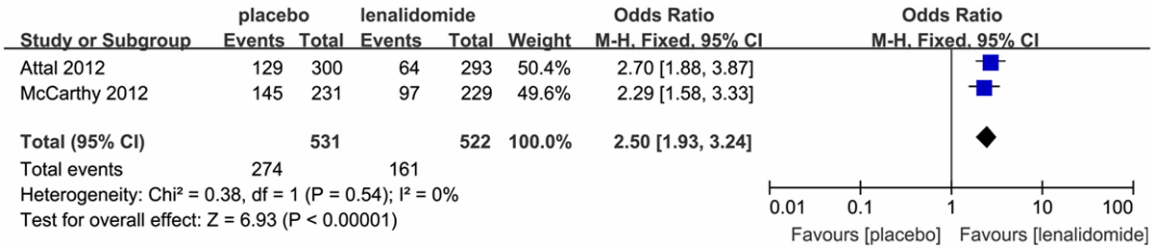

Figure 2. Pooled odd ratios of progression-free survival in the comparison of lenalidomide maintenance therapy arm and placebo maintenance therapy arm.

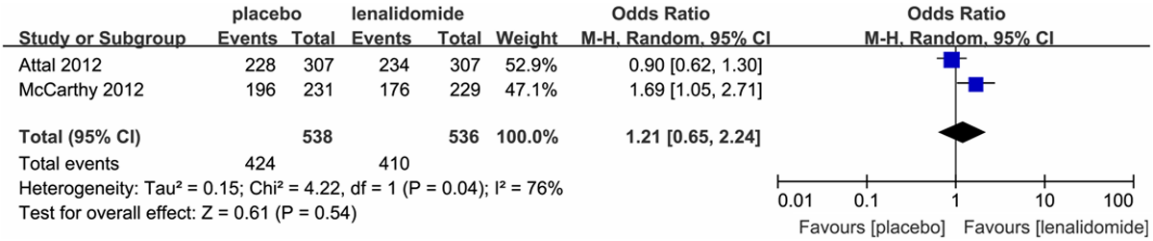

Figure 3. Pooled odd ratios of overall survival in the comparison of lenalidomide maintenance therapy arm and placebo maintenance therapy arm.

Survival

From the two trials, 1053 patients were evaluable for PFS. The pooled OR of PFS was 2.50 (95% CI = 1.93 to 3.24, P < 0.00001), showing marked benefit of lenalidomide maintenance for improving PFS, with no statistically significant heterogeneity (P = 0.54, I^2 = 0%, **Figure 2**). Both trials were eligible for analysis of OS (1074 patients). Although there was a trend toward increased OS with lenalidomide, a random-effects statistical model revealed that there was no statistically significant difference in OS between lenalidomide maintenance therapy arm and placebo maintenance therapy arm (OR = 1.21, 95% CI = 0.65 to 2.24, P = 0.54). Significant heterogeneity existed between the two trials (P = 0.04, I^2 = 76%, **Figure 3**).

Adverse events

The incidence of adverse events was reported in both trials. As shown in **Figure 4**, we found significant differences between lenalidomide and placebo arms, with more patients in the lenalidomide arm experiencing greater incidence of neutropenia (OR = 4.88, 95% CI = 3.67 to 6.50), infection (OR = 2.82, 95% CI = 1.67 to 4.73), hematologic cancers (OR = 3.31, 95% CI = 1.30 to 8.41), and solid tumors (OR = 2.24, 95% CI = 1.01 to 4.98). No significant differences between lenalidomide and placebo arms were seen with deep vein thrombosis (OR = 2.15, 95% CI = 0.92 to 5.06), peripheral neuropathy (OR = 1.50, 95% CI = 0.53 to 4.25), thrombocytopenia (OR = 1.05, 95% CI = 0.12 to 9.54), or anemia (OR = 1.36, 95% CI = 0.02 to 83.86). Among all the adverse events, significant heterogeneity was seen only with thrombocytopenia (P < 0.0001, I^2 = 93%) and anemia (P = 0.0001, I^2 = 93%).

Discussion

The efficacy and safety of lenalidomide maintenance therapy after ASCT in patients with MM has been in question. In order to address the issue, we conducted a meta-analysis of two randomized double-blind placebo-controlled studies encompassing 1074 patients treated with lenalidomide or placebo maintenance therapy after ASCT. We confirmed that lenalidomide maintenance therapy markedly improved PFS. However, this did not translate into an evident benefit, as OS was not significantly improved. Notably, there was significant heterogeneity of OS in these trials, which may have emerged for several reasons. First was potential difference in patient factors, such as cytogenetic abnormalities. A detailed analysis of patient population characteristics in relation to OS benefit should be investigated. The second

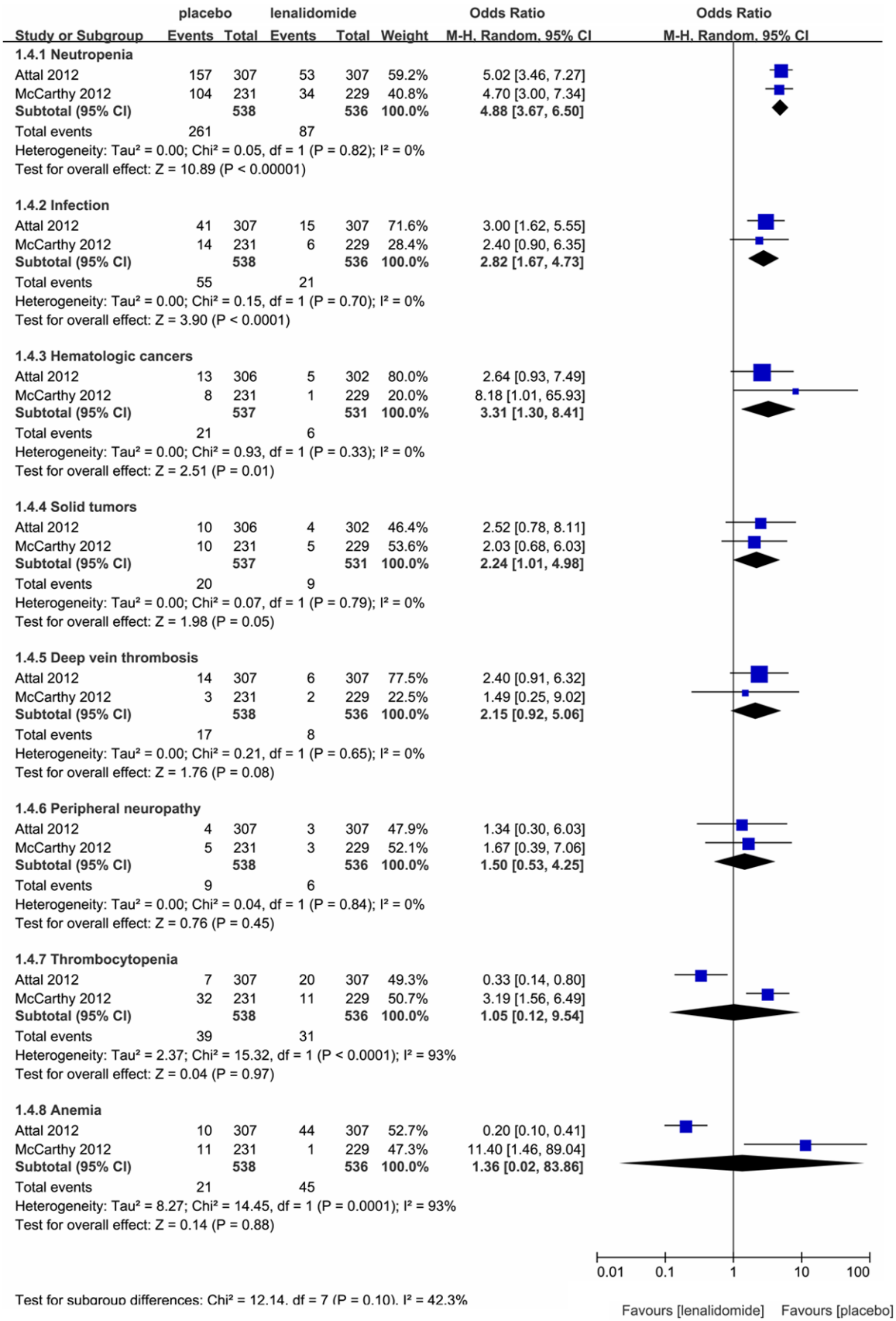
placebo
lenalidomide
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
1.4.1 Neutropenia
Attal 2012 157 307 53 307 59.2% 5.02 [3.46, 7.27]
McCarthy 2012 104 231 34 229 40.8% 4.70 [3.00, 7.34]
Subtotal (95% CI) 538 536 100.0% 4.88 [3.67, 6.50]
Total events 261 87
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%
Test for overall effect: Z = 10.89 (P < 0.00001)
1.4.2 Infection
Attal 2012 41 307 15 307 71.6% 3.00 [1.62, 5.55]
McCarthy 2012 14 231 6 229 28.4% 2.40 [0.90, 6.35]
Subtotal (95% CI) 538 536 100.0% 2.82 [1.67, 4.73]
Total events 55 21
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 1 (P = 0.70); I² = 0%
Test for overall effect: Z = 3.90 (P < 0.0001)
1.4.3 Hematologic cancers
Attal 2012 13 306 5 302 80.0% 2.64 [0.93, 7.49]
McCarthy 2012 8 231 1 229 20.0% 8.18 [1.01, 65.93]
Subtotal (95% CI) 537 531 100.0% 3.31 [1.30, 8.41]
Total events 21 6
Heterogeneity: Tau² = 0.00; Chi² = 0.93, df = 1 (P = 0.33); I² = 0%
Test for overall effect: Z = 2.51 (P = 0.01)
1.4.4 Solid tumors
Attal 2012 10 306 4 302 46.4% 2.52 [0.78, 8.11]
McCarthy 2012 10 231 5 229 53.6% 2.03 [0.68, 6.03]
Subtotal (95% CI) 537 531 100.0% 2.24 [1.01, 4.98]
Total events 20 9
Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.79); I² = 0%
Test for overall effect: Z = 1.98 (P = 0.05)
1.4.5 Deep vein thrombosis
Attal 2012 14 307 6 307 77.5% 2.40 [0.91, 6.32]
McCarthy 2012 3 231 2 229 22.5% 1.49 [0.25, 9.02]
Subtotal (95% CI) 538 536 100.0% 2.15 [0.92, 5.06]
Total events 17 8
Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 1 (P = 0.65); I² = 0%
Test for overall effect: Z = 1.76 (P = 0.08)
1.4.6 Peripheral neuropathy
Attal 2012 4 307 3 307 47.9% 1.34 [0.30, 6.03]
McCarthy 2012 5 231 3 229 52.1% 1.67 [0.39, 7.06]
Subtotal (95% CI) 538 536 100.0% 1.50 [0.53, 4.25]
Total events 9 6
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%
Test for overall effect: Z = 0.76 (P = 0.45)
1.4.7 Thrombocytopenia
Attal 2012 7 307 20 307 49.3% 0.33 [0.14, 0.80]
McCarthy 2012 32 231 11 229 50.7% 3.19 [1.56, 6.49]
Subtotal (95% CI) 538 536 100.0% 1.05 [0.12, 9.54]
Total events 39 31
Heterogeneity: Tau² = 2.37; Chi² = 15.32, df = 1 (P < 0.0001); I² = 93%
Test for overall effect: Z = 0.04 (P = 0.97)
1.4.8 Anemia
Attal 2012 10 307 44 307 52.7% 0.20 [0.10, 0.41]
McCarthy 2012 11 231 1 229 47.3% 11.40 [1.46, 89.04]
Subtotal (95% CI) 538 536 100.0% 1.36 [0.02, 83.86]
Total events 21 45
Heterogeneity: Tau² = 8.27; Chi² = 14.45, df = 1 (P = 0.0001); I² = 93%
Test for overall effect: Z = 0.14 (P = 0.88)
0.01
0.1
1
10
100
Test for subgroup differences: Chi² = 12.14, df = 7 (P = 0.10), I² = 42.3%
Favours [lenalidomide]
Favours [placebo]

Figure 4. Pooled odd ratios of adverse events (neutropenia, infection, hematologic cancers, solid tumors, deep vein thrombosis, peripheral neuropathy, thrombocytopenia, and anemia) in the comparison of lenalidomide maintenance therapy arm and placebo maintenance therapy arm.

was the difference in induction and consolidation therapy before transplantation. Whether lenalidomide was effective as maintenance therapy after already having been used during induction or/and consolidation therapy needed be investigated. Additionally, the discontinuation of maintenance therapy in the Attal et al. Trial and the early study unblinding and crossover in the McCarthy et al. Trial may also have contributed to the heterogeneity.

It was possible that the increase in adverse events also contributed to the observed lack of OS benefit with lenalidomide therapy after ASCT. The difference between the lenalidomide and placebo maintenance arms was not significant for deep vein thrombosis, peripheral neuropathy, thrombocytopenia, and anemia. However, neutropenia, infection, hematologic cancers and solid tumors events were more frequent in those receiving lenalidomide maintenance therapies. These were serious adverse events that should be carefully monitored at regular intervals through blood counts and tumor biomarkers. Perhaps OS could be improved through earlier intervention against these adverse events.

While not without limitations, our stringent, combined analysis contributes to our understanding of lenalidomide as a maintenance therapy. The most obvious limitation was that only two studies met the inclusion criteria. Also, our work was only based on aggregate study, not on analysis of individual patient data, and is therefore limited in time-to-event analyses. Nevertheless, the several strengths of our meta-analysis outweigh the limitations. First, the quality of a meta-analysis is always subject to the quality of the included studies and the studies used in our meta-analysis were selected based on strict criteria and were both of high quality. Both trials were large RCTs that reported double blinding of the participants and outcome assessors and used an intention-to-treat analysis and described power analysis. Second, the efficacy and safety outcomes were defined similarly in both the individual trials included in our meta-analysis. Furthermore, the present study was the first systematic review to evaluate specifically the efficacy and safety of lenalidomide maintenance therapy after ASCT in patients with MM.

In summary, we showed that lenalidomide maintenance therapy for patients with MM after ASCT improved PFS. However, treatment-related adverse events must be closely monitored and longer follow-up and additional high quality RCTs were needed to evaluate the effects of lenalidomide maintenance on OS.

Acknowledgements

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Disclosure of conflict of interest

None.

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