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Review Article

Efficacy and safety of subcutaneous bortezomib versus intravenous bortezomib in patients with multiple myeloma: a systematic review and meta-analysis

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Abstract: Purpose: To compare the efficacy and safety of subcutaneous (SC) bortezomib versus intravenous (IV) bortezomib in multiple myeloma (MM) patients. Methods: A systematic literature search was performed from databases including the Cochrane Library, Embase, Medline, the Chinese National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Service System (CBM) and Wan Fang Database. Odds ratio (OR), and 95% confidence interval (CI) were calculated by RevMan 5.3. Subgroup analysis and publication bias were also conducted. Results: The meta-analysis included seven randomized controlled trials and six retrospective cohort studies, altogether involving 1,198 patients. Patients in SC administration group had lower risk of peripheral neuropathy (PN), both all grades (OR = 0.40, 95% CI 0.27 to 0.59, $P < 0.001$) and 3-4 grades (OR = 0.45, 95% CI 0.25 to 0.82, $P < 0.001$). Complete response (CR) and overall response rate (ORR) had no significant differences between the two groups (OR = 0.78, 95% CI 0.56 to 1.10, $P = 0.17$; OR = 0.82, 95% CI 0.63 to 1.07, $P = 0.14$, respectively). Conclusion: The efficacy of SC bortezomib was similar to IV bortezomib for MM patients and has a significant improved safety profile.

Keywords: Bortezomib, multiple myeloma, subcutaneous, intravenous, peripheral neuropathy, meta-analysis

Introduction

Bortezomib is the first proteasome inhibitor which has become an important part of the standard chemotherapy for recurrent or newly diagnosed multiple myeloma (MM) [1]. This novel agent has brought significant survival benefits for patients, but adverse events (AEs) are inevitable such as peripheral neuropathy (PN), myelosuppression, fatigue and diarrhea, which may decrease patients' quality of life and influence their acceptance of treatment [2-4]. Recently, multiple studies have reported that subcutaneous administration can offer non-inferior efficacy compared with standard intravenous (IV) administration, but with an improved safety profile [5]. Because of the small number of patients in these studies, the efficacy and safety of SC bortezomib have not been well defined. Therefore, we conducted d a systematic review and a meta-analysis to compare the efficacy and safety of SC bortezomib versus IV bortezomib for treating MM patients.

Methods

Search strategy

We searched the databases of the Cochrane Library, Embase, Medline, China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Service System (CBM) and Wan Fang Database to collect relevant studies designed to compare the efficacy and safety of SC versus IV bortezomib in MM patients. No language restriction was used. The following basic search terms were used: LDP-341, bortezomib, Velcade, multiple myeloma, intravenous administration, subcutaneous administration. The search was performed on 10 September 2016.

Inclusion criteria

Studies that met the following criteria were included in our study: (1) randomized control clinical trials or retrospective cohort study. (2) reporting the efficacy and safety of SC versus IV

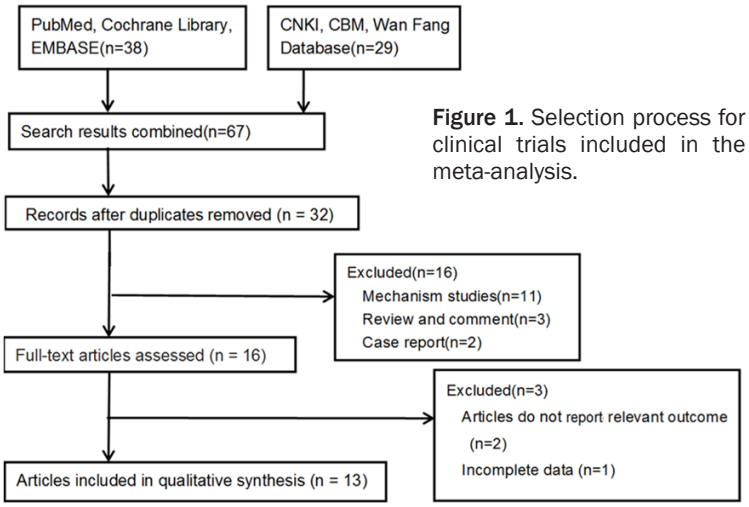

Figure 1. Selection process for clinical trials included in the meta-analysis.

bortezomib in MM patients. (3) including at least one of the following outcomes: complete response (CR), overall response rate (ORR) and AEs. (4) providing sufficient data to calculate odds ratio (OR) with 95% confidence interval (CI).

Data extraction

As for each included study, the following information was extracted: first author, published year, published language, country, type of study, patients, chemotherapy, outcomes (CR, ORR, all grades and 3-4 grades AEs). The AEs were assessed by the National Cancer Institute Common Toxicity Criteria in each group. Data extraction was performed by two independent reviewers (Shilong Zhang and Jing Li) and any disagreements were resolved through consensus with a third reviewer (Peng Liu).

Evaluation of study quality

We adopted the criteria of the Cochrane risk of bias tool to assess the quality of the included randomized control clinical trials. And the Newcastle Ottawa quality assessment tool (NOS) was used to evaluate the quality of the included retrospective cohort studies [6].

Statistical analysis

Statistical analyses were performed by RevMan5.3. CR, ORR and AEs were analyzed using dichotomous variables and their 95% CI. I^2 was used to test the heterogeneity. $I^2 > 50\%$ and $P < 0.1$ indicated significant heterogeneity between the included studies. And thus a random-effects statistical model was used. Otherwise a fixed-effects model was used ($I^2 < 50\%$ and $P > 0.1$) [7]. In addition, subgroup analysis based on the type of study (randomized control clinical trial, retrospective cohort study) was performed to explore the potential source of heterogeneity. A funnel plot was created to test the publication bias. All *P* values were two-sided.

Results

Selection of studies

As shown in **Figure 1**, primary searches found out 67 relative studies that described the SC administration of bortezomib in MM patients. Of them, we firstly excluded 35 studies because they were duplications. Of the 32 publications that remained, we finally abandoned other 16 studies for the following reasons: mechanism studies; review and comment; case report; lack of relevant outcome; incomplete data. At the end of the identification process, 13 studies were considered eligible for our analysis.

Characteristics of included studies

Of the included studies, seven were randomized controlled trials [8, 9, 13, 15, 16, 18, 19], six were retrospective cohort studies [10-14, 17, 20] and all of them were published between 2008 and 2016. Seven was published in Chinese [10, 12, 13, 17-20], and the other six were in English [8, 9, 11, 14-16]. The number of patients in the included studies ranged from 24 to 290. The detailed characteristics of the included studies were presented in **Table 1**.

Evaluation of study quality

The results of the quality assessment were shown in details in **Tables 2** and **3**. Four randomized controlled trials [8, 9, 16, 18] mentioned the use of random sequence generation, but only two of them described the methods [9, 16]. Two of the randomized controlled trials applied allocation concealment [15, 16]. No studies performed or mentioned blinding methods. All of the randomized controlled trials used the intent-to-treat analysis. For retrospective cohort studies, the average NOS score was 7.0.

Table 1. Characteristics of the included studies

Authors	Year	Language	Country	Type of study	Patients	Chemotherapy	Outcomes
Moreau [8]	2008	English	France	RCT	Newly	B*9 cyc	a, b, c, d
Moreau [9]	2011	English	France	RCT	Recurrent	B*8 cyc	a, b, c, d, e
Liu [10]	2013	Chinese	China	RCS	Newly	PAD (cyc: NR)	a, b, c, d, e
Lamm [11]	2013	English	Austria	RCS	Newly	VDT*5 cyc	a, b, c
Qin [12]	2014	Chinese	China	RCS	NR	BCD*4 cyc	a, b, d
Yan [13]	2014	Chinese	China	RCT	NR	BAD (cyc: NR)	a, b, d
Minarik [14]	2015	English	Czech	RCS	NR	NR	a, b, d
Wu [15]	2015	English	China	RCT	Newly	VTD*8 cyc	a, b, c, e
Merz [16]	2015	English	Germany	RCT	Newly	PAD*3 cyc	a, e
Ding [17]	2015	Chinese	China	RCS	Recurrent	VAD (cyc: NR)	d
Lin [18]	2016	Chinese	China	RCT	NR	BCD (cyc: NR)	a, b, d
Zhang [19]	2016	Chinese	China	RCT	NR	BD*2 cyc	a, b, c, d, e
Xu [20]	2016	Chinese	China	RCS	NR	BAD*4 cyc	a, b, d

Abbreviation: RCT, randomized clinical trial; RCS, retrospective cohort study; B. bortezomib; A, adriamycin; C, cyclophosphamide; D, dexamethasone; P, prednisolone; V, vincristine; T, thalidomide; NR, not reported. a, CR; b, ORR; c,myelosuppression; d, PN; e, diarrhea.

Table 2. Quality evaluation of the included randomized controlled trials by Cochrane risk of bias tool

Study	Radom sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete Outcome data	Selective reporting	Other bias
Moreau [8]	LRB	URB	HRB	HRB	LRB	LRB	LRB
Moreau [9]	LRB	URB	HRB	HRB	LRB	LRB	LRB
Yan [13]	URB	URB	URB	HRB	LRB	LRB	LRB
Wu [15]	URB	LRB	LRB	HRB	LRB	LRB	LRB
Merz [16]	LRB	LRB	LRB	HRB	LRB	LRB	LRB
Lin [18]	LRB	HRB	HRB	HRB	LRB	LRB	LRB
Zhang [19]	URB	HRB	HRB	HRB	LRB	LRB	LRB

Abbreviation: LRB, low risk of bias; HRB, high risk of bias; URB, unclear risk of bias.

Table 3. Quality evaluation of the included retrospective cohort studies by Newcastle-Ottawa Scale

Study	Selection	Comparability	Exposure or outcome	Total score
Liu [10]	▲▲	▲▲	▲▲▲▲	8
Lamm [11]	▲▲	▲▲▲	▲▲▲▲	9
Qin [12]	▲▲	▲▲	▲▲	6
Minarik [14]	▲▲▲	▲▲	▲▲	7
Ding [17]	▲	▲▲	▲▲	5
Xu [20]	▲▲	▲▲	▲▲▲	7

Four of them were considered to be of high quality [10, 11, 14, 20], scoring higher than seven points.

Meta-analysis of CR and ORR

Twelve studies [8-16, 18-20] reported the data of CR. The pooled result showed that there was no significant difference between SC administration group and IV administration group, and no heterogeneity among the studies (OR = 0.78, 95% CI 0.56 to 1.10, P = 0.17, I^2 = 0%) (**Figure 2**). What is more, as shown in **Figure 3**, patients with SC administration had a similar ORR compared with those with IV administration, which indicated SC bortezomib was as effective as IV bortezomib among MM patients (RR = 0.82, 95% CI 0.63 to 1.07, P = 0.14, I^2 = 0%).

Meta-analysis of AEs

In the included studies, we analyzed several common AEs such as PN, neutropenia, throm-

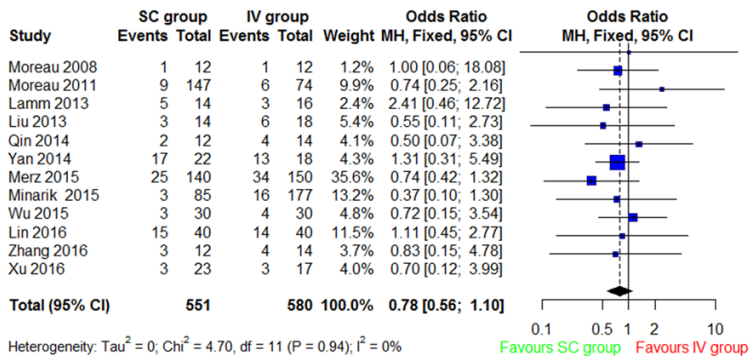

Figure 2. Meta-analysis of data on CR in SC group and IV group.

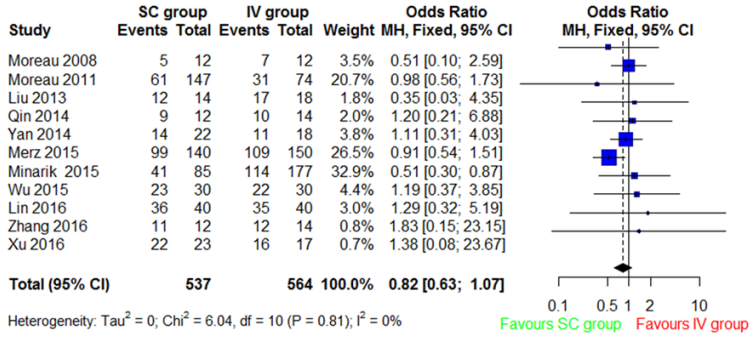

Figure 3. Meta-analysis of data on ORR in SC group and IV group.

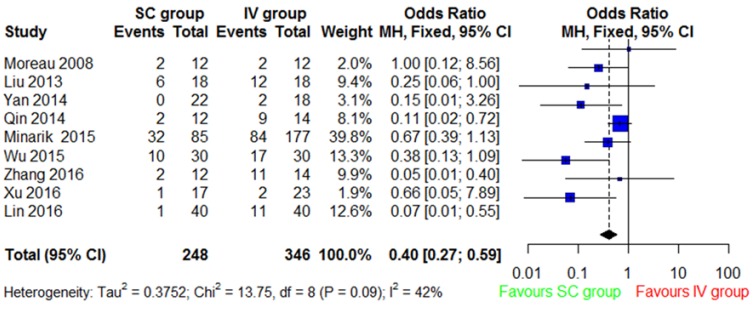

Figure 4. Meta-analysis of data on all grades PN in SC group and IV group.

bocytopenia and diarrhea. For all grades AEs, SC administration could significantly decrease the risk of PN (OR = 0.40, 95% CI 0.27 to 0.59, $P < 0.001$, $I^2 = 42\%$) (**Figure 4**). However, no significant differences were observed in neutropenia (OR = 0.76, 95% CI 0.54 to 1.07, $P = 0.11$, $I^2 = 22\%$), thrombocytopenia (OR = 0.76, 95% CI 0.45 to 1.27, $P < 0.0001$, $I^2 = 0\%$) and diarrhea (OR = 0.69, 95% CI 0.47 to 1.01, $P = 0.06$, $I^2 = 8\%$) (Supplementary Figure 1). In addition, similar results were found in analysis of 3-4 grades AEs. The risk of PN (OR = 0.45, 95% CI 0.25 to 0.82, $P < 0.001$, $I^2 = 0\%$) (**Figure 5**) was obviously lower in the SC administration group. There were no statistically significant differences in neutropenia (OR = 0.73, 95% CI 0.48 to 1.11, $P = 0.14$, $I^2 = 17\%$), thrombocytopenia (OR = 0.76, 95% CI 0.45 to 1.27, $P < 0.0001$, $I^2 = 0\%$) and diarrhea (OR = 0.57, 95% CI 0.57 to 1.25, $P = 0.16$, $I^2 = 49\%$) between the two groups (Supplementary Figure 2).

Subgroup analysis

According to the studies were randomized clinical or retrospective cohort studies, we conducted the subgroup analysis of CR, ORR and PN. And no different results were found in these outcomes (**Table 4**).

Publication bias analysis

The CR data reported in most of the included studies was used to create a funnel plot. As **Figure 6** showed, the funnel plot seemed to be asymmetrical and indicated that there may be publication bias, which would affect the stability of our results. In addition, Egger's test confirmed again the publication bias ($P < 0.05$).

Discussion

Bortezomib can intercept various cell signaling pathways through inhibiting the 20S proteasome complex and exerts its anticancer effect [21-23]. During the past decade, bortezomib has shown great survival benefit in recurrent or newly diagnosed MM patients, but many adverse events limit its application, especially peripheral neuropathy, which is the most significant one of factors why patients decrease or discontinue bortezomib [24]. IV injection is the standard route of bortezomib administration [25]. However, it usually requires repeated

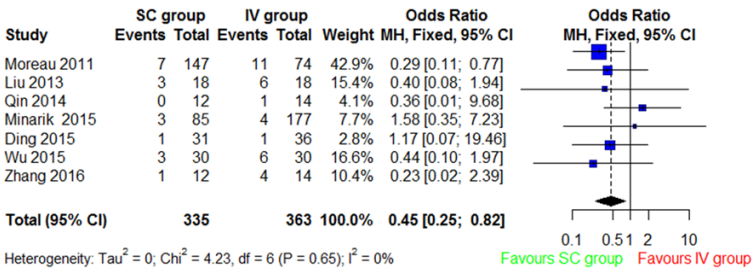

Figure 5. Meta-analysis of data on 3-4 grades PN in SC group and IV group.

Table 4. Subgroup analysis of outcomes based on randomized clinical trial and retrospective cohort studies

Comparison	Pooled OR	95% CI	*P*	I^2
CR				
Studies with RCS	0.78	0.12-3.99	0.17	0
Studies without RCS	0.89	0.69-1.16	0.39	0
ORR				
Studies with RCS	0.80	0.62-1.04	0.14	0
Studies without RCS	0.93	0.85-1.03	0.15	2
All-grade PN				
Studies with RCS	0.40	0.27-0.59	< 0.001	42
Studies without RCS	0.36	0.22-0.60	< 0.001	39
Grade ≥ 3 PN				
Studies with RCS	0.45	0.25-0.82	0.01	0
Studies without RCS	0.36	0.18-0.72	0.04	0

Abbreviation: OR, odds ratio; CI, confidence interval; RCS, retrospective cohort study; CR, complete response; ORR, overall response rate; PN, peripheral neuropathy.

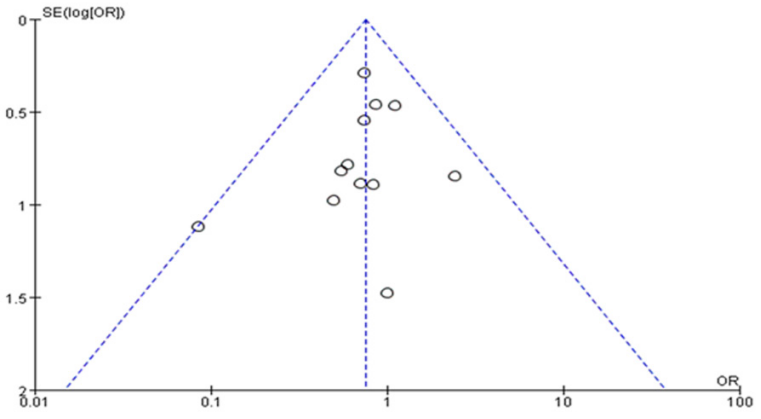

Figure 6. The funnel plot for estimating publication bias of CR in the meta-analysis.

intravenous injections or insertion of long-term central venous catheters and is associated with some serious adverse events. In recent years, SC administration has been gradually applied to the clinic for the treatment of MM due to its relatively mild adverse events [26, 27]. The objective of an ideal administration is to improve survival outcomes with minimal adverse events and without reducing patients' quality of life. Therefore, we carried out this meta-analysis to evaluate the efficacy and safety of SC bortezomib in MM patients.

Thirteen studies with a total of 1,198 patients were included in our analysis. Neither significant CR nor ORR difference was observed in our pooled results. And it indicated that the efficacy of SC bortezomib was comparable to standard IV route for CR and ORR in MM patients. In addition, according to an analysis of a multicenter, randomised phase III study, no significant difference for PFS was observed between the two administration routes, showing that SC bortezomib and IV bortezomib has also the same effect as for long-term survival. However, it should be noted that we were not able to pool the PFS and OS for further long-term survival analysis because few of the included studies had provided the information about them.

The underlying mechanism of the similar efficacy between SC bortezomib group and IV bortezomib group may be explained by pharmacodynamic and pharmacokinetic analyses. Moreau et al. have demonstrated that the efficacy of bortezomib is associated with the overall systemic exposure. Compared with IV route, the maximum plasma concentration (Cmax) of SC

route is lower and the time to Cmax of SC route is longer as well, but the overall systemic exposure of bortezomib is almost identical between them. Similarly, Although SC route takes a longer time to arrive at the maximum percentage inhibition of 20S proteasome activity, the area under the effect-time curve (AUC) were also comparable, which indicates that there was no significant difference in pharmacokinetics between the two routes [28]. In addition, the pharmacokinetic and pharmacodynamic parameters are independent of SC injection sites and thickness of subcutaneous fat [29].

Regarding the safety of SC administration, our analysis showed significant differences between two administration routes. Consistent with previous studies, peripheral neuropathy was the most frequent adverse event in our study, and SC administration could significantly reduce the risk of both all grades and 3-4 grades peripheral neuropathy. In addition, no significant differences were found in neutropenia, thrombocytopenia and diarrhea at all grades and 3-4 grades. In contrast to systemic adverse events, mild and transient adverse reactions around the injection site, including pain, swelling, itching and redness, are more common with SC administration routes. They occur more frequently in the first cycle of SC administration of bortezomib in the thigh and are less common with IV injections [30]. In this study, we failed to compare the risk of these local injection site reactions between the two routes for lack of corresponding data in the included studies. Hence, more efforts should be made to monitor the local injection site reactions of SC administration.

Besides reducing the risk of various adverse events, SC administration has the advantages of patient convenient and low price [31, 32]. It can help shorten the time in hospital, save medical expense and raise the degree of satisfaction of patients [26]. Moreover, results form a prospective single-center study indicate that SC administration could favor home administration of the drug, with a substantially reduced cost and greatly improved patient compliance [33], and this is very beneficial to patients who have to undergo long-term treatment, particularly for those who have experienced severe adverse events or have problems in venous access.

Although we conducted this meta-analysis through a standardized process, it also had some limitations. First, of the included studies, almost half of them were retrospective. So the quality of evidence was relatively modest for all the pooled results. Additionally, the chemotherapy regimens were not the same in all arms, and it might be another major source of heterogeneity. Second, most of the studies were published in Chinese, and publication bias may exist across the included studies. Third, although there were thirteen studies with 1,198 patients, the samples in some studies were relatively small and might have less sufficient statistical power to evaluate the efficacy and safety of SC bortezomib in MM patients. Finally, lack of long-term follow-up made it difficult to analysis the long-term effects of SC administration of bortezomib. Despite these limitations, our study still provided credible evidence to support that SC route can help optimize the administration of bortezomib for MM patients.

In conclusion, this meta-analysis demonstrated that SC administration of bortezomib offered a similar efficacy to the standard IV administration but significantly reduced the risk of peripheral neuropathy. In addition, SC administration is associated with substantial reduced cost and improved quality life in MM patients, particularly in patients who experience severe adverse events or have poor vascular condition.

Disclosure of conflict of interest

None.

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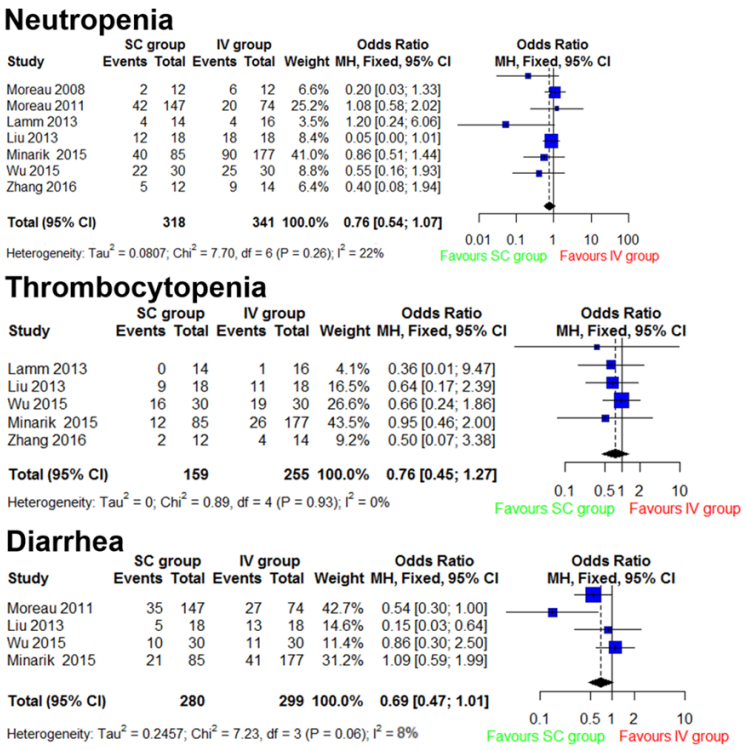
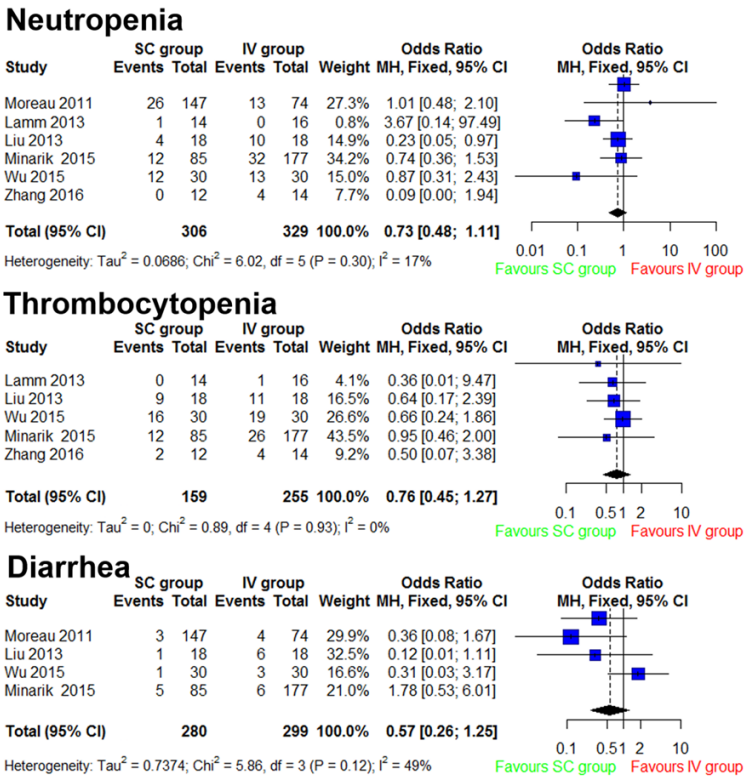


Supplementary Figure 1. Meta-analysis of data on all grades AEs in SC group and IV group.



Supplementary Figure 2. Meta-analysis of data on 3-4 grades AEs in SC group and IV group.