The efficacy and safety of thalidomide-based therapy in patients with advanced non-small cell lung cancer: a meta-analysis

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Several randomized controlled clinical trials have compared therapy with or without thalidomide in the treatment of advanced non-small cell lung cancer (NSCLC). However, these studies did not produce consistent results. We carried out a meta-analysis to determine the efficacy and safety of thalidomide-based therapy in patients with advanced NSCLC. For this meta-analysis, we selected randomized clinical trials that compared thalidomide in combination with other therapy or other therapy alone in patients with advanced NSCLC. The outcomes included median overall survival (OS), one- and two-year survival, tumor response, and toxicities. Hazard ratios (HRs) or risk ratios (RRs) were reported with 95% confidence intervals (CIs). A total of 5 eligible trials were included for the meta-analysis, with 729 patients in the thalidomide group and 711 patients in the control group. Compared with non-thalidomide-based therapy, patients receiving thalidomide plus other therapy did not differ significantly in terms of one- and two-year survival or tumor response (RR = 1.32, 95% CI: 0.66–2.63, p = 0.43; RR = 1.22, 95% CI: 0.48–3.11, p = 0.68; RR = 1.05, 95% CI: 0.92–1.19, p = 0.51, respectively). However, thalidomide-based therapy induced more grade 3–4 dizziness and constipation (RR = 2.05, 95% CI: 1.10–3.81, p = 0.02; RR = 4.78, 95% CI: 1.84–12.38, p = 0.001, respectively). The addition of thalidomide to other therapy did not improve survival and tumor response in patients with advanced NSCLC, and thalidomide-based therapy was associated with more grade 3/4 dizziness and constipation.

Key words: carcinoma, non-small cell lung, meta-analysis, thalidomide.

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Introduction

Lung cancer is one of the most common cancers in the world. In 2011, it is estimated that approximately 221,000 new cases were diagnosed, and about 156,900 deaths occurred in the United States [1]. Among all lung cancer cases, non-small cell lung cancer (NSCLC) represents approximately 70–80% with locally advanced disease accounting for about 25–30% and metastatic disease approximately 40–50% [2]. For locally advanced NSCLC patients, the current standard care is combined chemo-radiotherapy, which can offer 8–17% 5-year survival [3]. However, for patients with metastatic NSCLC, the median survival using platinum-based treatment is about 8 to 10 months. Although the therapeutic strategy in advanced NSCLC has radically changed in the last few years, the curative effect seems to have reached a plateau [4]. Therefore, novel treatment options are urgently needed.

In recent years, angiogenesis, an essential molecular biological event in many physiologic as well as pathologic processes including oncogenesis and progression of cancer [5], has evoked a huge interest from clinicians and scientists. The vascular endothelial growth factor (VEGF) pathway plays a key role in tumor angiogenesis. VEGF binds to some receptors existing in host vascular endothelial cells, monocytes and hematopoietic precursors, and then stimulates endothelial cell proliferation, differentiation, migration and survival [6]. VEGF is expressed in the majority of NSCLC and elevated expression is associated with early postoperative relapse and short survival [7–11]. The anti-VEGF antibody bevacizumab in combination with platinum-based chemotherapy has been identified as improving the survival in patients with advanced nonsquamous NSCLC [12]. Thalidomide is an oral anti-angiogenic agent, which has achieved success in treating multiple myeloma. The advantages of thalidomide include convenient administration, lower costs and immunomodulatory properties [13, 14]. A study in mice showed that thalidomide can suppress tumor growth [15], and many phase II trials have indicated that thalidomide was well tolerated and has potential to improve survival in patients with advanced NSCLC [16–18]. Therefore, several randomized controlled clinical trials comparing therapy with or without thalidomide in the treatment of advanced NSCLC have been launched. However, these studies did not produce consistent results. To provide a relatively reliable basis for clinical rational drug use, we conducted a meta-analysis to evaluate the efficacy and safety of thalidomide-based therapy in patients with advanced NSCLC.

Material and methods

Search strategy

A literature search was performed in Medline, Embase, the Cochrane Library, Chinese Biomedical Literature Database, China Journal Full-text Database and Chinese Scientific Journals Database in September, 2012. No restriction was set for languages. The search strategy was based on the following Medical Subject Heading terms (MeSH) and text words: "thalidomide" AND ("non-small cell lung cancer" OR "lung cancer" OR "lung neoplasm" OR "NSCLC").

Data extraction

Relevant articles and abstracts were selected and reviewed independently by two of the authors (Ying Liu and Shuhua He). Any discrepancies in data quality scores and abstraction were assessed further and resolved by consensus. The main extracted data included: 1) first author's last name, the year of publication; 2) the number of patients allocated and characteristic of patients (clinical stage); 3) the interventional measures used (anticancer drugs, RT dose/Fraction in Gy, RT methods and thalidomide dose/course); 4) the outcome of the trials including the tumor response rate, median overall survival (OS), one-year survival and two-year survival rate plus adverse events.

Quality assessment

Each study was evaluated for quality using the previously validated Jadad 5-point scale to assess randomization (0–2 points), double blinding (0–2 points) and withdrawals and dropouts (0–1 point) [19]. Concealment of allocation was assessed as adequate, inadequate or unclear.

Inclusion criteria

The publications included in the meta-analysis fulfill the following criteria: 1) trials must compare thalidomide combined with other therapy to other therapy alone for treating advanced NSCLC; 2) the trials were described as randomized controlled trials (RCTs); 3) patients must be diagnosed and confirmed cytologically or pathologically, with no previous chemotherapy or radiotherapy for their cancer; 4) outcome measures were survival and tumor response for the calculation of the risk ratio (RR) at a 95% confidence interval (CI).

Exclusion criteria

The following studies were excluded: 1) studies lacking control groups; 2) those with no clearly reported outcomes of interest; 3) those RCTs in which SCLC patients were recruited; 4) review articles, letters, comments and case reports; 5) studies investigating tumor response only, without survival.

Outcome measures

The outcome measures consist of survival, tumor response, and adverse events. Survival included one-year and two-year survival rate. Based on the degree of tumor regression, the efficacy of treatment (using the WHO "Response Evaluation Criteria in Solid Tumors" [20]) could be defined as: CR (complete response, CT and/or MRI revealed complete clearance of the lesion); PR (partial response, lesion decreased ≥ 50%); SD (lesion decreased less than 50% or increased less than 25%); PD (size of lesion increased more than 25% after treatment). Based on the comparison of abdominal CT or MRI before and after treatment, tumor responses are evaluated as CR + PR.

Statistical analysis

Data from RCTs meeting inclusion criteria were valuated with the Cochrane software Review Manager Version 5.1. For time-to-event data, the log HR and its variance were summarized using previously reported methods [21]. Dichotomous data were compared using relative risks (RRs). Respective 95% CI was calculated for each estimate and presented in forest plots.

Statistical heterogeneity among studies was assessed using the χ^2 test and I^2 statistic [22]. If $P \leq 0.1$ and $I^2 > 50\%$, the heterogeneity was considered significant, then the Mantel-Haenszel random-effects model was used to analyze the treatment groups. The fixed-effect model Mantel-Haenszel method was used if there was no evidence of heterogeneity ($p > 0.1$, or $p < 0.1$ but $I^2 \leq 50\%$) between studies. Statistical significance was $p < 0.05$. Publication bias was visually evaluated by the "funnel plot" method and statistically by Egger's test [23]. Subgroup analysis was performed to detect the effects of patients with different TNM stage.

Results

Study characteristics

The database search strategy initially retrieved 236 publications, and 60 were excluded due to duplication (Table 1 and Table 2). English [24, 25] (n = 2) and Chinese [26–28] (n = 3) language publications met the study's inclusion criteria. These publications included patients receiving thalidomide-based therapy (n = 729) and non-thalidomide-based therapy (n = 711) (Fig. 1).

Quality assessment

The methodological quality of studies is reported in Table 3. Three trials [25, 27, 28] explicitly stated the method of randomization, whereas the other studies did not provide this information. Two trials [25, 26] were described with the term "double blinding" and there was no evidence of allocation concealment. Three trials [24, 25, 27] reported withdrawals and excluded these from the analysis. There were no studies with incomplete outcome data, early stoppage bias, or baseline imbalances. Based on the rating system, the quality of most trials was poor, which might influence the results of the analysis.

Meta-analysis outcomes

Median overall survival

Only two trials [24, 25] reported HRs for median OS. Meta-analysis indicated that the HR for OS favored non-thalidomide-based therapy (HR = 2.94, 95% CI: 2.61–3.32, $p < 0.00001$), without evidence of heterogeneity between the studies ($I^2 = 20\%$, $p = 0.26$) (Fig. 2). The pooled HR was performed using the fixed-effect model.

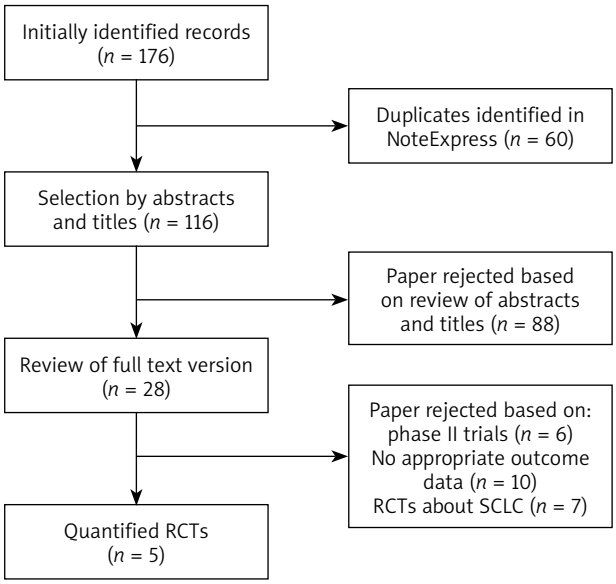
Table 1. Characteristics of included randomized controlled trials (RCTs)

Author (year)	Treatment modality	No. of patients	TNM stage	Median OS (months)	Survival rate (%)		Tumor response (%)			
					1 year	2 year	CR	PR	SD	PD
Hoang, T 2012	chemoradiotherapy thalidomide	271	IIIA IIIB	16			2.7	35.5	36.3	14.3
	chemoradiotherapy placebo	275	IIIA IIIB	15.3			4.2	30.8	40.8	12.3
Lee, SM 2009	chemotherapy thalidomide	372	IIIB IV	8.5	35	12	40[a]			
	chemotherapy placebo	350	IIIB IV	8.9	38	16	42[a]			
He, QS 2008	chemotherapy thalidomide	19	IIIB IV	10.0	31.6	5.3	0	31.5	21.1	47.4
	chemotherapy placebo	20	IIIB IV	9.0	25	0	0	30	10	60
Jiang, WM 2010	chemotherapy thalidomide	31	IIIB IV	10.0			45.1[a]			
	chemotherapy placebo	30	IIIB IV	9.2			40[a]			
He, HJ 2011	chemoradiotherapy thalidomide	36	IIIA IIIB		77.78	47.22	44.44[a]			
	chemoradiotherapy placebo	36	IIIA IIIB		66.67	22.22	22.22[a]			

[a]*CR + PR*

Table 2. Features of interventional measures

Author	Chemotherapy agents	Radiotherapy	Thalidomide
Hoang, T	Paclitaxel 225 mg/m^2 and carboplatin area under the curve (AUC) 6 followed by 60 Gy thoracic radiation administered concurrently with weekly paclitaxel 45 mg/m^2 and carboplatin AUC 2	Linear accelerator photon beams of at least 6 MeV energy were delivered to the lung tumor and nodal disease at 2-Gy per fraction per day for 30 fractions, five fractions per week, over 6 weeks. D_T 60 Gy	The starting dose of thalidomide was 200 mg, which was subsequently increased by 100 mg every week as tolerated up to a total daily dose of 1,000 mg
Lee, SM	Gemcitabine 1,200 mg/m^2 intravenous (days 1) and 8 of 21-day cycle) and carboplatin area under the curve 5 or 6, dependent on method of glomerular filtration rate estimation (day 1), for a maximum of 4 cycles		The starting dose was 100 mg/d and, if tolerated, increased to 150 mg/d at the end of chemotherapy for 1 month, then to 200 mg/d continued for the rest of the trial
He, QS	Navelbine 25 mg/m^2 intravenous (days 1 and 8 of 21-day cycle) and cisplatin 30 mg/m^2 intravenously guttae (day 1-3) for a maximum of 4 cycles		The starting dose was 100 mg/d and, if tolerated, increased by 50 mg every week up to 200 mg/d for three months.
Jiang, WM	Gemcitabine 1,000 mg/m^2 intravenous (days 1 and 8 of 21-day cycle) and cisplatin 20 mg/m^2 intravenously guttae (day 1-4 of 21-day cycle) for a maximum of 4 cycles		The dose was 200 mg/d (day 1–60)
He, HJ	Docetaxel 75 mg/m^2 (days 1) and cisplatin 25–30 mg/m^2 intravenously guttae (day 1–4 of 21-day cycle) for a maximum of 4–6 cycles	Concurrent conformal radiation using 6 MV or X-ray to the lung tumor and nodal disease at 2.0–2.2 Gy per fraction per day. D_T 64–66 Gy	The starting dose was 100 mg/d for a week and, if tolerated, increased to 150 mg/d at the beginning of the second week and continued for at least two months



RCT – randomized controlled trial

Fig. 1. Procedures used for trial selection

One-year survival

Three trials [25, 27, 28] reported one-year survival data. Meta-analysis for 1-year survival showed that thalidomide-based therapy had a comparable 1-year survival with non-thalidomide-based therapy (RR = 1.32, 95% CI: 0.66–2.63, p = 0.43; heterogeneity p = 0.001). Examining the data in Table 1 indicated that He [27] included IIIA stage patients, which could contribute to statistical heterogeneity. To test this hypothesis, subgroup analyses showed that statistical heterogeneity disappeared (heterogeneity p = 0.99), and the pooled RRs for 1-year survival showed there was no statistical difference between the two groups (Fig. 3).

Two-year survival

Three trials [25, 27, 28] were identified with outcome measurements of two-year survival. Meta-analysis showed there was no statistical difference in two-year survival between thalidomide-based therapy and non-thalidomide-based therapy (RR = 1.22, 95% CI: 0.48–3.11, p = 0.68; heterogeneity p = 0.03). As with one-year survival, we dropped the He, HJ [27] trial and the pooled RRs also showed no statistical difference between two groups (RR = 0.72, 95% CI: 0.49–1.07, p = 0.10; heterogeneity p = 0.35) (Fig. 4).

Tumor response (CR + PR)

All five trials [24–28] reported tumor response data. The pooled RR indicated that there was no statistical significance when thalidomide-based therapy was compared with non-thalidomide-based therapy (RR = 1.05, 95% CI: 0.92–1.19, p = 0.51) (Fig. 5). The fixed-effect model was used because of no heterogeneity between the studies (I^2 = 12%, p = 0.34).

Adverse events

As shown in Figures 6–7, we analyzed grade 3–4 adverse events including hematologic toxicity such as leucopenia, neutropenia, and thrombocytopenia, and non-hematologic toxicity such as nausea or vomiting, rash, constipation and thromboembolic events between thalidomide-based-therapy and non-thalidomide-based therapy. Four trials [24–26, 28] reported leucopenia, three trials [24–26] reported thrombocytopenia, and two trials [24, 25] reported neutropenia, nausea/vomiting, rash, constipation, dizziness, and thrombosis/embolism. Thalidomide-based therapy and non-thalidomide-based therapy did not differ significantly in leucopenia, neutropenia and thrombocytopenia (RR = 1.15, 95% CI: 0.89–1.48, p = 0.29; RR = 1.08, 95% CI: 0.91–1.28, p = 0.37; RR = 0.91, 95% CI: 0.71–1.18, p = 0.49, respectively). Regarding non-hematologic toxicity, compared with non-thalidomide-based therapy, there was a significant increase in constipation and rash (RR = 2.05, 95% CI: 1.10–3.81, p = 0.02; RR = 4.78, 95% CI: 1.84–12.38, p = 0.001, respectively), but no statistically significant difference in dizziness, thrombosis/embolism and nausea/vomiting (RR = 1.56, 95% CI: 0.78–3.11, p = 0.21; RR = 3.36, 95% CI: 0.57–19.92, p = 0.18; RR = 0.83, 95% CI: 0.49–1.39, p = 0.48, respectively) was observed. The random-effect model was used for thrombosis/embolism toxicity because of heterogeneities (I^2 = 68%, p = 0.08). There was no significant heterogeneity for other adverse event analyses.

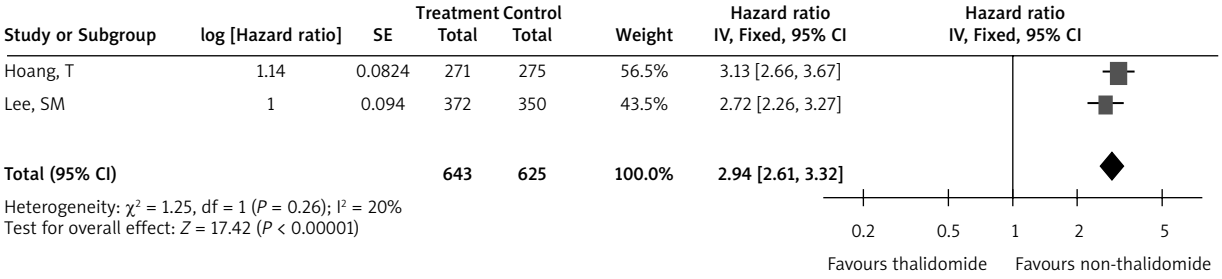
Table 3. Methodological quality of included studies

Study	Randomization State	Randomization method described	Double-blinding State	Double-blinding method described	Description of withdrawals/ dropouts[a]	Jadad score[b]	Allocation concealment
Hoang, TM	√	unclear	X	NA	adequate	2	unclear
Lee, SM	√	adequate	√	adequate	adequate	5	adequate
He, QS	√	adequate	X	NA	inadequate	3	unclear
Jiang, WM	√	inadequate	√	inadequate	inadequate	2	unclear
He, HJ	√	adequate	X	NA	adequate	3	unclear

NA – not applicable, check mark – yes, X – no

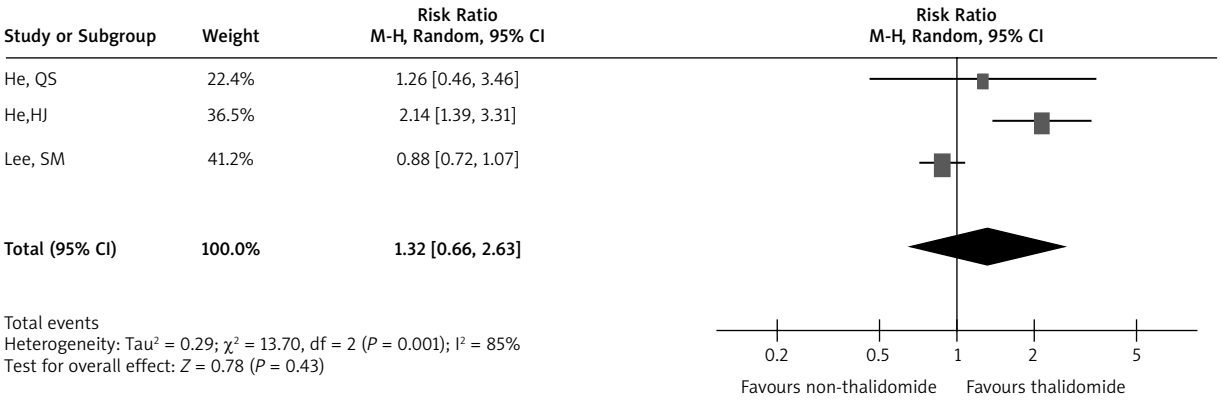
[a]To be graded as "adequate", the description must include the number and reasons for withdrawals in each group; if there were no withdrawals, it must be stated in the article

[b]Described by Jadad et al. [19]



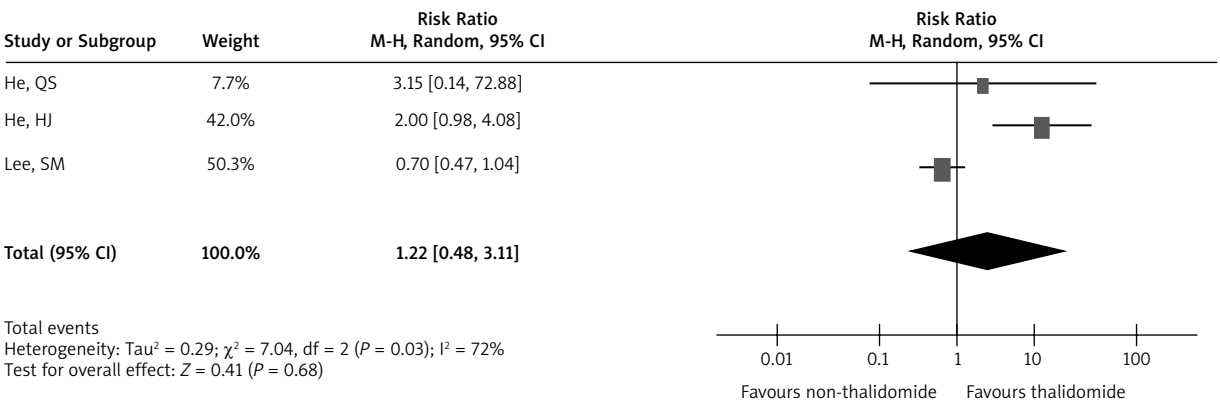
SE – standard error, IV – inverse variance, CI – confidence interval

Fig. 2. Comparison of overall survival between thalidomide and non-thalidomide based therapy



M-H – Mantel-Haenszel, CI – confidence interval

Fig. 3. Comparison of two-year survival between thalidomide and non-thalidomide based therapy



M-H – Mantel-Haenszel, CI – confidence interval

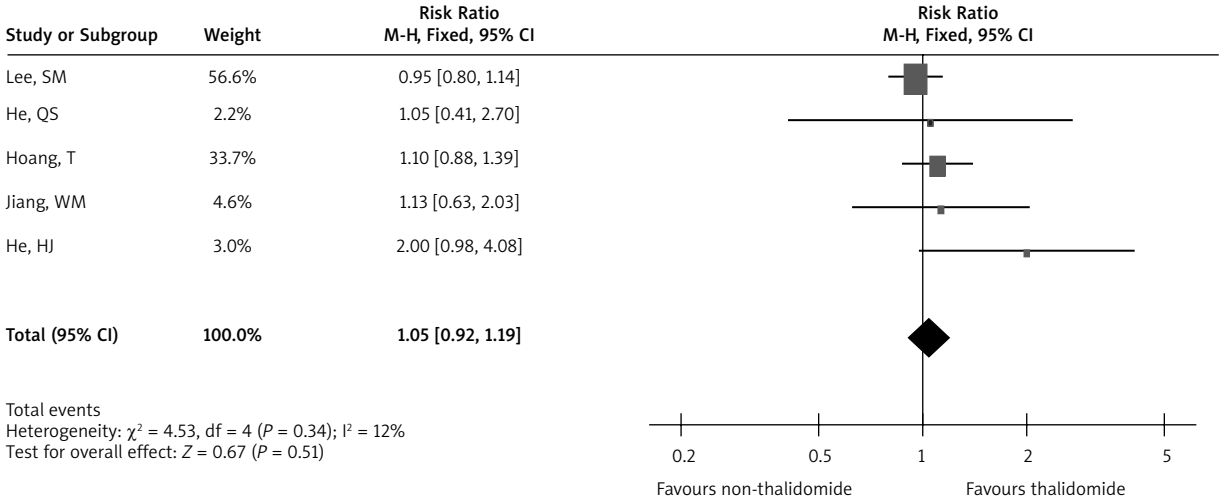
Fig. 4. Comparison of two-year survival between thalidomide and non-thalidomide based therapy

Publication bias

The funnel plot for the comparison of tumor response was visually symmetrical (Fig. 8), which indicated that our meta-analysis was not affected by publication bias. Quantitative Begg's test and Egger's test did not find evidence of publication bias ($P_{Begg's}$ = 0.806, $P_{Egger's}$ = 0.222) for tumor response.

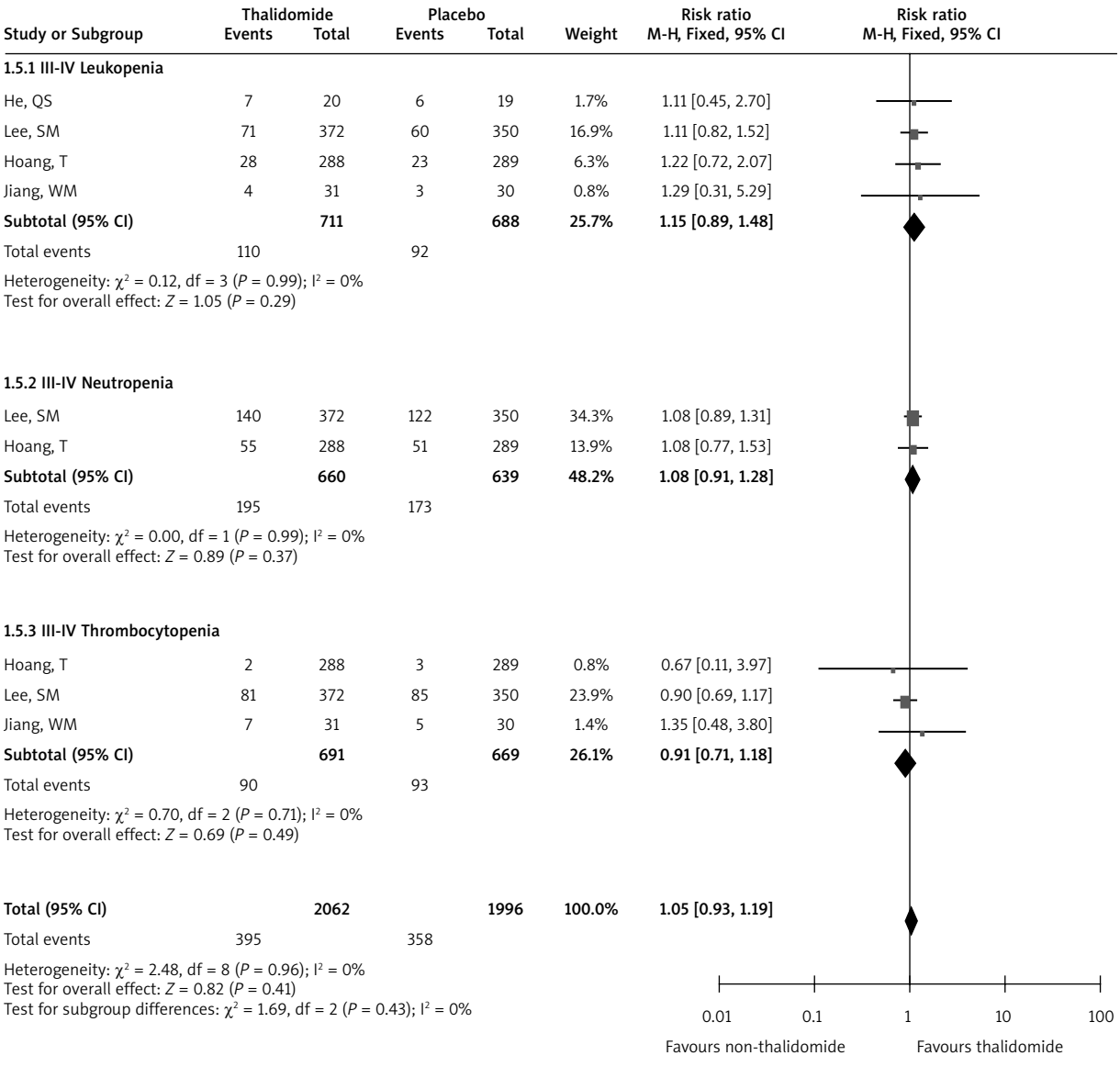
Discussion

The vascular endothelial growth factor and its receptor system play a key role in tumor angiogenesis; therefore, angiogenic inhibition has become a promising anti-cancer therapy. Some studies [29, 30] have shown that thalidomide inhibits angiogenesis by interfering with basic fibroblast growth factor (bFGF) and/or VEGF. A phase II study [18] explored the safety of combining thalidomide with carboplatin and paclitaxel for stage IIIA, IIIB, or IV NSCLC and indicated that this therapy was well tolerated and supported further investigation. Another trial [16] combining thalidomide with irinotecan and gemcitabine showed that this combination is active in advanced NSCLC with a manageable toxicity profile. In 2008, He *et al.* [28] reported that thalidomide plus vinorelbine and cisplatin increase the tumor response and median overall survival. After that, some randomized controlled trials [26, 27] demonstrated that thalidomide-based combined therapies improve response and do not increase the toxicity in treatment of



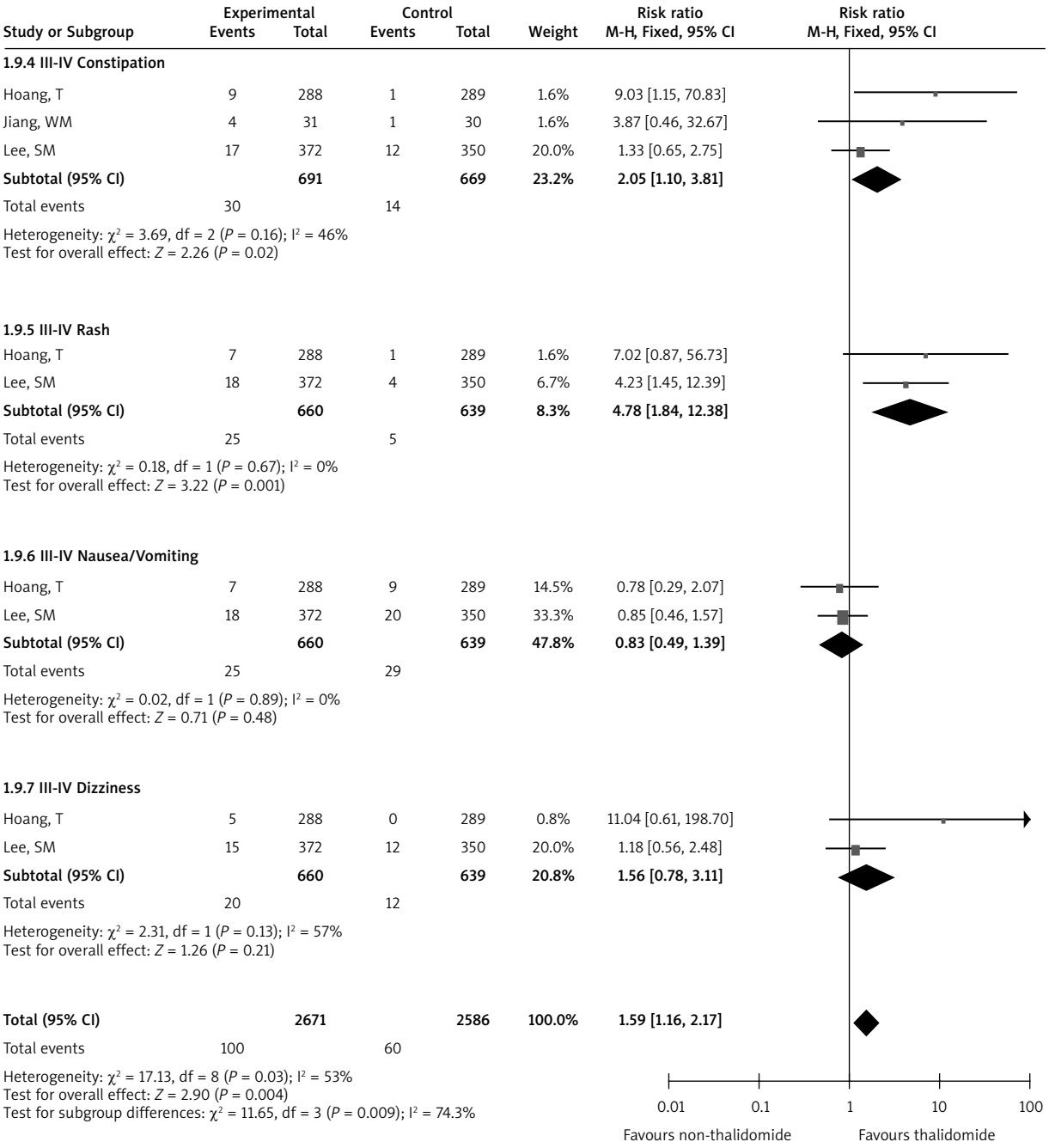
M-H – Mantel-Haenszel, CI – confidence interval

Fig. 5. Comparison of tumor response between thalidomide and non-thalidomide based therapy



M-H – Mantel-Haenszel, CI – confidence interval

Fig. 6. Summary of grade 3–4 hematological toxicity



M-H – Mantel-Haenszel, CI – confidence interval

Fig. 7. Summary of grade 3–4 nonhematological toxicity

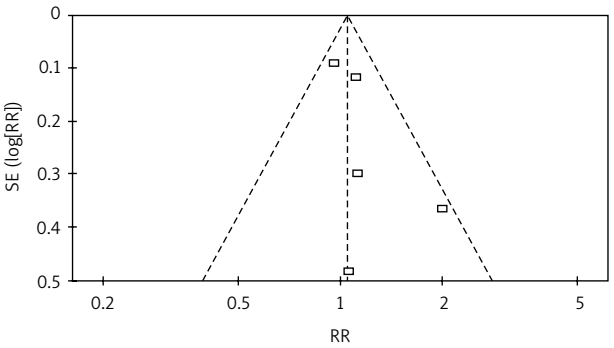


Fig. 8. Funnel plot for comparison of tumor response

patients in advanced NSCLC. However, Lee *et al.* [25] performed a randomized, double-blind, placebo-controlled trial and found no difference in progression-free survival or overall survival when thalidomide was added to gemcitabine and carboplatin. Another phase III trial [24] evaluated the efficacy of carboplatin, paclitaxel and radiotherapy with or without thalidomide for stage III NSCLC and concluded that the addition of thalidomide to chemo-radiotherapy increased toxicity but did not improve survival in patients with locally advanced NSCLC. Therefore, we conducted a meta-analysis to provide a relatively objective evaluation of the efficacy and safety of thalidomide-based therapy in patients with advanced NSCLC.

In our meta-analysis, we found that whether thalidomide was used or not used in combination with conventional treatment, there was no significant difference in terms of one- and two-year survival or tumor response. However, a significant increase of median OS was found in non-thalidomide based therapy. We found that trials analyzed for OS had a large sample size while some small sample trials were included when the one- and two-year survival and tumor response were evaluated, which might induce a difference outcome. Among these trials, only Lee *et al.* [25] reported that thalidomide might benefit those with squamous histology. Because it was a retrospective analysis, those data were not sufficient to claim proof, but only to generate hypotheses for further study. In terms of the association between dose of thalidomide and effect, when Hoang *et al.* [24] increased the dose from 100 mg/day up to 1000 mg/day it did not seem more effective, which was consistent with other studies investigating the dose response relationship in multiple myeloma [31] and small-cell lung cancer [32, 33]. Regarding grade 3–4 toxicity data, our pooled analysis showed that the addition of thalidomide to chemotherapy or chemo-radiotherapy did not increase bone marrow toxicity such as leucopenia or neutropenia but induced a higher rate of grade 3 or greater non-hematologic toxicities including dizziness, constipation, rash and thromboembolic events. Among these non-hematologic toxicities, venous thromboembolic events (VTE) such as deep venous thrombosis (DVT) and pulmonary embolus (PE) are a common and headache-causing toxicity associated with thalidomide. A meta-analysis [34] reported that patients on thalidomide are 2.6 times more likely to develop VTE, and patients on combination therapy with thalidomide and dexamethasone are eight times more likely to develop VTE. Therefore, in 2007, the American Society of Clinical Oncology recommended that myeloma patients treated with thalidomide and chemotherapy or dexamethasone receive either low-molecular weight heparins or warfarin (to an international normalized ratio of ~1.5) as prophylaxis against VTE [35]. However, in the ECOG 3598 study [24], taking low-dose aspirin daily did not prevent or reduce the incidence of thromboembolic events.

Several limitations in our study should also be noted. First, not all the included RCTs described methods of randomization and adequate allocation concealment, that is, many were of low quality; secondly, three of the available trials are of small sample size, which may lead to a small-study effect, in which reported effects are larger [36]; thirdly, some trials did not report all the relevant data, which might influence the result; finally, a stratified analysis of histology type was not performed in this meta-analysis because efficiency and survival data of certain types of cancer were not reported in trials. Actually, similar with bevacizumab, histologic type might affect survival in NSCLC. Therefore, although thalidomide-based therapy showed no significant difference in one- and two-year survival or tumor response in this meta-analysis, owing to the lack of stratified analysis according to histology type, clinical application of these results should be cautious, especially for squamous cell lung cancer.

In conclusion, based on the results of our meta-analysis, thalidomide plus other therapy did not improve the one and two-year survival or tumor response in patients with advanced NSCLC, and thalidomide-based therapy was associated with more grade 3/4 dizziness and constipation. Physicians should be aware of the risks associated with thalidomide, and balance therapeutic benefits with adverse events.

Authors declare no conflict of interest.

References

1. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin 2011; 61: 212-36.
2. Pérol M, Arpin D. Angiogenesis and lung cancer. Bull Cancer 2007; 94 Spec No: S220-S31.
3. Furuse K, Fukuoka M, Kawahara M, Nishikawa H, Takada Y, Kudoh S, Katagami N, Ariyoshi Y. Phase iii study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage iii non-small-cell lung cancer. J Clin Oncol 1999; 17: 2692-9.
4. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002; 346: 92-8.
5. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell 2000; 100: 57-70.
6. Ferrara N. Vascular endothelial growth factor: basic science and clinical progress. Endocr Rev 2004; 25: 581-611.
7. Mattern J, Koomägi R, Volm M. Association of vascular endothelial growth factor expression with intratumoral microvessel density and tumour cell proliferation in human epidermoid lung carcinoma. Br J Cancer 1996; 73: 931-4.
8. Fontanini G, Faviana P, Lucchi M, et al. A high vascular count and overexpression of vascular endothelial growth factor are associat-

ed with unfavourable prognosis in operated small cell lung carcinoma. Br J Cancer 2002; 86: 558-63.
9. Yuan A, Yu CJ, Kuo SH, Chen WJ, Lin FY, Luh KT, Yang PC, Lee YC. Vascular endothelial growth factor 189 mRNA isoform expression specifically correlates with tumor angiogenesis, patient survival, and postoperative relapse in non-small-cell lung cancer. J Clin Oncol 2001; 19: 432-41.
10. Han H, Silverman JF, Santucci TS, Macherey RS, d'Amato TA, Tung MY, Weyant RJ, Landreneau RJ. Vascular endothelial growth factor expression in stage i non-small cell lung cancer correlates with neoangiogenesis and a poor prognosis. Ann Surg Oncol 2001; 8: 72-9.
11. Herbst RS, Onn A, Sandler A. Angiogenesis and lung cancer: prognostic and therapeutic implications. J Clin Oncol 2005; 23: 3243-56.
12. Reck M, von Pawel J, Zatloukal P, et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAil. J Clin Oncol 2009; 27: 1227-34.
13. Reyes-Terán G, Sierra-Madero JG, Martínez del Cerro V, Arroyo-Figueroa H, Pasquetti A, Calva JJ, Ruiz-Palacios GM. Effects of thalidomide on HIV-associated wasting syndrome: a randomized, double-blind, placebo-controlled clinical trial. AIDS 1996; 10: 1501-7.
14. Franks ME, Macpherson GR, Figg WD. Thalidomide. Lancet 2004; 363: 1802-11.
15. DeCicco KL, Tanaka T, Andreola F, De Luca LM. The effect of thalidomide on non-small cell lung cancer (NSCLC) cell lines: possible involvement in the PPARgamma pathway. Carcinogenesis 2004; 25: 1805-12.
16. Jazieh AR, Komrokji R, Gupta A, Patil S, Flora D, Knapp M, Issa M, Abdel Karim N. Phase II trial of thalidomide, irinotecan and gemcitabine in chemonaive patients with advanced non-small cell lung cancer. Cancer Invest 2009; 27: 932-6.
17. Miller AA, Case D, Atkins JN, Giguere JK, Bearden JD. Phase II study of carboplatin, irinotecan, and thalidomide in patients with advanced non-small cell lung cancer. J Thorac Oncol 2006; 1: 832-6.
18. Merchant JJ, Kim K, Mehta MP, Ripple GH, Larson ML, Brophy DJ, Hammes LC, Schiller JH. Pilot and safety trial of carboplatin, paclitaxel, and thalidomide in advanced non small-cell lung cancer. Clin Lung Cancer 2000; 2: 48-54.
19. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996; 17: 1-12.
20. Geyer HL, Viggiano RW, Lacy MQ, Witzig TE, Leslie KO, Mikhael JR, Stewart K. Acute lung toxicity related to pomalidomide. Chest 2011; 140: 529-33.
21. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 1998; 17: 2815-34.
22. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557-60.
23. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-34.
24. Hoang T, Dahlberg SE, Schiller JH, Mehta MP, Fitzgerald TJ, Belinsky SA, Johnson DH. Randomized phase III study of thoracic radiation in combination with paclitaxel and carboplatin with or without thalidomide in patients with stage III non-small-cell lung cancer: the ECOG 3598 study. J Clin Oncol 2012; 30: 616-22.
25. Lee SM, Rudd R, Woll PJ, et al. Randomized double-blind placebo-controlled trial of thalidomide in combination with gemcitabine and carboplatin in advanced non-small-cell lung cancer. J Clin Oncol 2009; 27: 5248-54.
26. Jiang WM, Wang Y, Jiang H, et al. The control clinical study on the treatment of advanced non-small cell lung cancer by TGP regimen and GP regimen. Chinese Clin Oncol 2009; 15: 798-801.
27 He HJ, Hu W. Efficacy evaluation of Thalidomide combined with chemoradiotherapy in the treatment of 36 cases with NSCLC stage III. J Chinese Oncol 2011; 17: 202-4.
28. He QS, Yi T, Luo B, Zhang X. A randomized trial of NVB plus DDP with versus without thalidomide in the treatment of advanced non small cell lung cancer. Zhongguo Fei Ai Za Zhi 2008; 11: 264-7.
29. Paravar T, Lee DJ. Thalidomide: mechanisms of action. Int Rev Immunol 2008; 27: 111-35.
30. D'Amato RJ, Loughnan MS, Flynn E, Folkman J. Thalidomide is an inhibitor of angiogenesis. Proc Natl Acad Sci U S A 1994; 91: 4082-5.
31. Yu Y, Xu X, Du Z, Shi M. Non-platinum regimens of gemcitabine plus docetaxel versus platinum-based regimens in first-line treatment of advanced non-small cell lung cancer: a meta-analysis on 9 randomized controlled trials. Cancer Chemother Pharmacol 2012; 69: 1265-75.
32. Riedel RF, Crawford J, Dunphy F, Herndon JE 2nd, Garst J, Kelley MJ. Phase II study of carboplatin, irinotecan, and thalidomide combination in patients with extensive stage small-cell lung cancer. Lung Cancer 2006; 54: 431-2.
33. Dowlati A, Subbiah S, Cooney M, et al. Phase II trial of thalidomide as maintenance therapy for extensive stage small cell lung cancer after response to chemotherapy. Lung Cancer 2007; 56: 377-81.
34. El Accaoui RN, Shamseddeen WA, Taher AT. Thalidomide and thrombosis. A meta-analysis. Thromb Haemost 2007; 97: 1031-6.
35. Lyman GH, Khorana AA, Falanga A, et al. American society of clinical oncology guideline: recommendations for venous thromboembolism prophylaxis and treatment in patients with cancer. J Clin Oncol 2007; 25: 5490-505.
36. Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. J Clin Epidemiol 2001; 54: 1046-55.

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