ORIGINAL RESEARCH

Angiogenesis inhibitors rechallenge in patients with advanced non-small-cell lung cancer: a pooled analysis of randomized controlled trials

Lingdi Zhao
Wei Li
Huiying Zhang
Nan Hou
Lanwei Guo
Quanli Gao

Department of Cancer Biotherapy, The Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, Henan Province, People's Republic of China

Purpose: Data on the role of angiogenesis inhibitors (AIs) rechallenge in the treatment of advanced non-small-cell lung cancer (NSCLC) patients who previously received bevacizumab remain limited. We aim to investigate the efficacy of AIs in the treatment of advanced NSCLC in this setting.

Methods: Studies from PubMed, Web of Science, and abstracts presented at American Society of Clinical Oncology meeting up to December 1, 2014 were searched to identify relevant studies. Eligible studies included prospective randomized controlled trials evaluating AIs in advanced NSCLC, with survival data on patients who previously received bevacizumab. The end points were overall survival and progression-free survival. Statistical analyses were conducted by using either random effects or fixed effect models according to the heterogeneity of included studies.

Results: A total of 452 patients with advanced NSCLC who previously received bevacizumab were identified for analysis. The meta-analysis results demonstrated that AI rechallenge significantly improved progression-free survival (hazard ratio: 0.72, 95% confidence interval: 0.58–0.89, P=0.002) when compared to non-AI containing regimens. Additionally, a nonsignificant improvement in overall survival was also observed in advanced NSCLC in this setting (hazard ratio: 0.82, 95% confidence interval: 0.65–1.03, P=0.087). Similar results were also observed in subgroup analysis according to treatment regimens.

Conclusion: The findings of this study suggest that NSCLC patients who relapsed after a first-line bevacizumab-containing chemotherapy obtain improved clinical benefits from AI rechallenge. Prospective clinical trials investigating the role of AI rechallenge in this setting are recommended.

Keywords: non-small-cell lung cancer, rechallenge, second-line, angiogenesis inhibitors, randomized controlled trials, meta-analysis

Correspondence: Quanli Gao
Department of Cancer Biotherapy, The Affiliated Cancer Hospital of Zhengzhou University, Number 127 Dongming Road, Jinshui District, Zhengzhou City 450008, Henan Province, People's Republic of China
Tel +86 371 6558 7098
Fax +86 371 6596 1505
Email gaoquanli2015@163.com

Introduction

Lung cancer is the leading cause of cancer-related mortality with an estimated 1.4 million deaths each year.[1] Non-small-cell lung cancer (NSCLC) accounts for 85% of the cases. Most of NSCLC patients have advanced disease at diagnosis. For these patients, platinum-based doublet therapy is the standard of care.[2] After the first-line failure, conventional monotherapy with docetaxel or pemetrexed, and more recently with erlotinib, gains a low response rate, patients have a relatively short progression-free survival (PFS) and overall survival (OS).[3–5] Clearly, novel therapeutic approaches to improve outcomes for patients with NSCLC are badly needed.[6]

Angiogenesis, the process of vasculature formation, is critical for tumor progression, invasion, and metastasis in solid tumors.[7] Pathways that promote angiogenesis

have been targeted as a therapeutic approach in multiple types of cancer, including NSCLC.[8–11] Of these, the vascular endothelial growth factor (VEGF) pathway has been the most well studied. Bevacizumab is the only approved antiangiogenic agent for NSCLC patients, when added to first-line carboplatin/paclitaxel chemotherapy.[12–14] More recently, the platelet-derived growth factor (PDGF) and fibroblast growth factor pathways have been identified as regulators of angiogenesis and potential mediators of resistance to VEGF inhibition. Thus, new antiangiogenic treatment strategies are being evaluated that target multiple receptors within a family (VEGF receptor [VEGFR]-1, VEGFR-2)[15–17] or multiple angiogenic pathways (targets VEGFR and PDGF receptor pathways).[15,18,19]

Several previously preclinical and observational studies demonstrate that sustained VEGF inhibition with bevacizumab can be beneficial in some patients with solid tumors.[20] Preclinical data suggest that sustained VEGF inhibition achieves and maintains tumor regression.[21–23] Rapid tumor revascularization has also been observed to occur after stopping the anti-VEGF therapy, indicating that vascular regrowth may be a normal physiological response to the stoppage of anti-VEGF therapy.[24,25] Sustained VEGF inhibition has thus been shown to achieve and maintain tumor regression. Insight into the effect of treatment with bevacizumab beyond disease progression has been provided by the randomized, prospective bevacizumab treatment trials known as the ML18147 study for metastatic colorectal cancer (mCRC).[26] In this prospective study, continued antiangiogenic treatment with bevacizumab plus chemotherapy beyond first progressive disease correlated with prolonged survival versus no continuation of bevacizumab (median OS: 11.1 versus 9.6 months). Thus, retreatment with angiogenesis inhibitors (AIs) could be proposed, hypothetically, for patients with NSCLC. However, in the NSCLC setting, no Phase III trials have been published in a second-line setting to prove the value of AIs rechallenge. In this study, we assess the effect on OS of AIs rechallenge in advanced NSCLC patients, who had previously been given bevacizumab plus standard first-line chemotherapy.

Materials and methods
Selection of studies
We searched the PubMed (data from January 2000 to October 2014), Embase (data from January 2000 to October 2014), and the Cochrane Library electronic databases. The search criteria included only randomized controlled trials (RCTs) which were published in English language, and

the key words "aflibercept", "VEGFR-TKIs", "sorafenib", "Nexavar", "sunitinib", "Sutent", "SU1248", "vandetanib", "Caprelsa", "ZD6474", "axitinib", "pazopanib", "Votrient", "GW786034", "regorafenib", "apatinib", "ramucirumab", "nintedanib", "BIBF1120", "thalidomide", "lenalidomide", "angiogenesis inhibitors", "randomized", "non-small-cell lung cancer" were used for the search. We also searched abstracts and virtual meeting presentations from the American Society of Clinical Oncology (http://www.asco.org/ASCO) conferences that took place between January 2004 and June 2014. Each publication was reviewed, and in cases of duplicate publication, only the most complete, recent, and updated report of the clinical trial was included for analysis. The authors confirm they did not require approvals and/or patient consent for these case studies.

Data extraction and clinical end point
Data extraction was conducted independently by two investigators according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement,[27] and any discrepancy between the reviewers was resolved by consensus. For each study, the following information was extracted: first author's name, year of publication, number of patients who received bevacizumab already, treatment arms, primary end points, and median follow-up. Phase I trials and single-group Phase II trials were omitted from analysis because of the lack of controls. Trials that met the following criteria were included in our analysis: 1) prospective randomized controlled trails comparing therapies with or without AIs (aflibercept, sorafenib, sunitinib, vandetanib, pazopanib, axitinib, regorafenib, apatinib, cediranib, ramucirumab, nintedanib, thalidomide, lenalidomide); 2) trials with patients who were pathologically confirmed to have NSCLC; and 3) studies having sufficient survival data of patients who received bevacizumab already. If multiple publications of the same trial were retrieved or if there was a case mix between publications, only the most recent publication (and the most informative) was included. The quality of reports of clinical trials was assessed and calculated using the 5-item Jadad scale, including randomization, double-blinding, and withdrawals as previously described.[28]

Data analysis
The analysis was undertaken on an intention-to-treat basis: patients were analyzed according to treatment allocated, irrespective of whether they received that treatment. Statistical analysis of the overall hazard ratio (HR) for OS and PFS was calculated using Version 2 of the Comprehensive

Meta-Analysis program (Biostat, Englewood, NJ, USA). A statistical test with a P-value less than 0.05 was considered significant. HR >1 reflects more deaths or progression in AIs-containing regimens group and vice versa. Between-study heterogeneity was estimated using the χ^2-based Q statistic.[29] The I^2 statistic was also calculated to evaluate the extent of variability attributable to statistical heterogeneity between trials. Heterogeneity was considered statistically significant when $P_{\text{heterogeneity}}$ <0.05 or I^2>50%. If heterogeneity existed, data were analyzed using a random effects model. In the absence of heterogeneity, a fixed effects model was used. To investigate the sources of heterogeneity, we also conducted predefined subgroup analysis according to treatment regimens. The presence of publication bias was evaluated by using the Begg and Egger tests.[30] All P-values were two sided. All confidence intervals (CIs) had a two-sided probability coverage of 95%.

Results
Search results
A total of 270 potentially relevant studies were retrieved electronically, 264 of which were excluded for the reasons shown in Figure 1. Six published RCTs with subgroup analysis assessing the efficacy of AIs rechallenge in NSCLC patients were included in the meta-analysis.[16,31–35] The baseline characteristics of each trial are presented in Table 1. A total of 452 patients were included in the study. According to the inclusion criteria of each trial, patients were required to have adequate renal, hepatic, and hematologic function. The quality of each included study was roughly assessed according to Jadad scale. All of the included trials were double-blind, placebo-controlled randomized trials, and thus had Jadad score of 5.
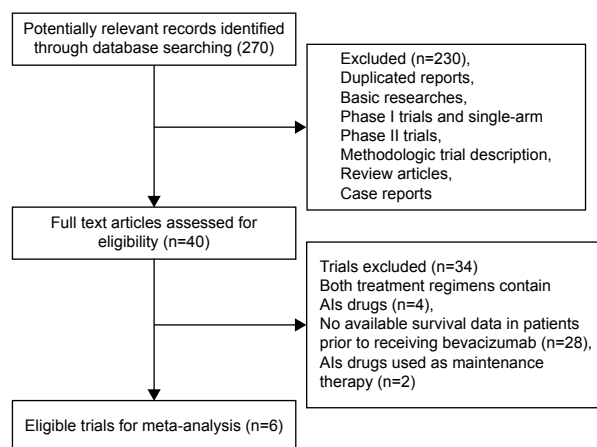

Figure 1 Studies eligible for inclusion in the meta-analysis.
Abbreviation: AIs, angiogenesis inhibitors.

Overall survival
All of the six trials reported OS data of AIs rechallenge in NSCLC patients who previously received bevacizumab. The pooled results demonstrated that AIs rechallenge had a tendency to improve OS in comparison with non-AIs-containing regimens (HR: 0.82, 95% CI: 0.65–1.03, P=0.087, Figure 2), using a fixed-effects model (I^2=0%, P=0.735). We then performed subgroup analysis according to treatment regimens and found that both AIs rechallenge plus chemotherapy (HR: 0.84, 95% CI: 0.63–1.12, P=0.24) or erlotinib (HR: 0.78, 95% CI: 0.53–1.14, P=0.20) had a tendency to improve OS when compared to non-AIs-containing regimens.

Progression-free survival
Six trials reported PFS data. The pooled HR for PFS demonstrated that AIs rechallenge significantly improved PFS, with a HR of 0.72 (95% CI: 0.58–0.89, P=0.002, Figure 3), compared with non-AIs containing therapy. There was no significant heterogeneity between trials (I^2=0%, P=0.49), and the pooled HR for PFS was performed by using fixed-effects model. We then did subgroup analysis according to treatment regimens and found that both AIs rechallenge plus chemotherapy (HR: 0.73, 95% CI: 0.57–0.95, P=0.018) or erlotinib (HR: 0.70, 95% CI: 0.48–1.00, P=0.05) regimens significantly improved PFS when compared with non-AIs-containing regimens.

Publication bias
Begg's funnel plot and Egger's test were performed to assess the publication bias of literatures. The Begg's funnel plots did not reveal any evidence of obvious asymmetry (P=0.70 for OS and P=0.06 for PFS, respectively). Then, Egger's test was used to provide statistical evidence of funnel plot symmetry. The results still did not suggest any evidence of publication bias for OS (P=0.53). However, there was publication bias for PFS using Egger's test (P=0.009). The difference in the results obtained from the two methods might be due to a greater statistical power of the regression methods.[36]

Discussion
The mechanism of resistance to chemotherapy is typically the result of changes in tumor cell biology and is often agent-specific.[37] By contrast, the mechanism of resistance for bevacizumab is not well understood, which might result from the development of alternative angiogenesis pathways.[38] Consequently, failure of chemotherapy does not necessarily mean failure of antiangiogenic treatment, implying that the disease may still be partially or significantly
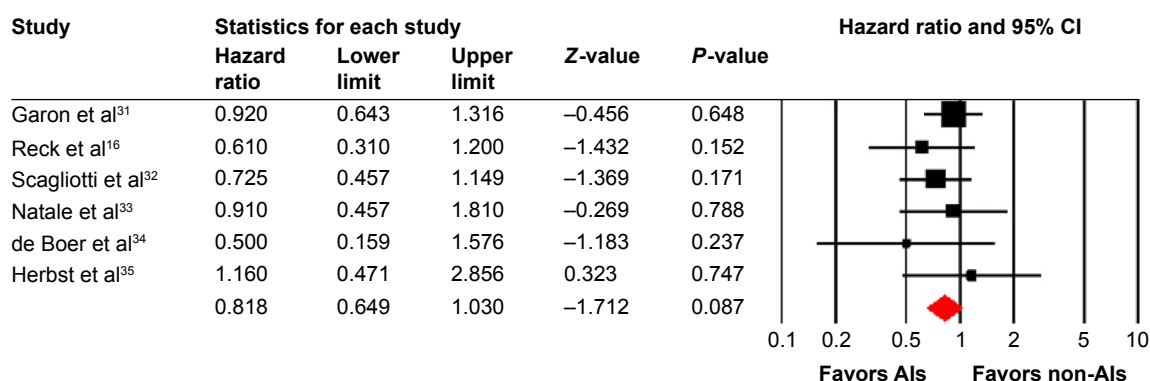
Table 1 Baseline characteristic of the six trials included for analysis

Study	Total patients	Number of patients who received bevacizumab already	Treatment regimens	Primary end point	Median follow-up (month)	Jadad score
Garon et al[31]	1,253	180	Ramucirumab 10 mg/kg + docetaxel Placebo + docetaxel	OS	9.5	5
Reck et al[16]	562	38	Nintedanib 200 mg qd po + docetaxel Placebo + docetaxel	PFS	7.1	5
Scagliotti et al[32]	960	96	Sunitinib 17.5 mg qd po + erlotinib Placebo + erlotinib qd po	OS	21.3	5
Natale et al[33]	1,240	50	Vandetanib 300 mg qd po + erlotinib Placebo + erlotinib	PFS	NR	5
de Boer et al[34]	534	44	Vandetanib 100 mg qd po + pemetrexed Placebo + pemetrexed	PFS	NR	5
Herbst et al[35]	1,391	44	Vandetanib 100 mg qd po + docetaxel Placebo + docetaxel	PFS	12.8	5

Abbreviations: OS, overall survival; PFS, progression-free survival; qd, four times a day; po, oral administration; NR, not reported.

dependent on VEGF-mediated endothelial cell mitogenesis and survival. The angiogenic signal continues throughout the lifespan of the tumor. One hypothesis is that persistent VEGF suppression, along with secondary and tertiary cytotoxic regimens, may result in continued clinical benefit. This hypothesis is supported by the experience of patients with mCRC enrolled in the bevacizumab ML18147 study.[26] In addition, the use of angiogenesis inhibitor aflibercept in patients with mCRC, previously treated with oxaliplatin-based regimen, also significantly improved OS when compared to chemotherapy alone (13.5 versus 12.06 months, *P*=0.0032).[39] Based on these considerations, we conducted the current meta-analysis to evaluate whether AIs rechallenge in combination with standard treatment versus standard of care alone in second-line treatment could obtain clinical benefits in NSCLC patients who have progressed after first-line treatment with bevacizumab-containing chemotherapy.

To the best of our knowledge, this study is the first meta-analysis with a focus on investigating the value of AIs rechallenge in pretreated patients with advanced NSCLC, who have been previously exposed to bevacizumab. This study included six RCTs, incorporating 452 patients who previously received bevacizumab. The pooled results confirm that AIs rechallenge significantly improve PFS compared to non-AIs-containing regimens. Additionally, there is a tendency of improved OS in AIs rechallenge groups. Similar results are observed in subgroup analysis according to treatment regimens. Therefore, this study suggests that, in patients with advanced NSCLC who previously received bevacizumab, AIs rechallenge in combination with standard treatment could be a preferable treatment option over standard second-line therapy alone, although this recommendation cannot be conclusive because the overall comparisons are not based on randomization. Furthermore, the toxicity outcome is not assessed.

Study	Statistics for each study					Hazard ratio and 95% CI
	Hazard ratio	Lower limit	Upper limit	*Z*-value	*P*-value	
Garon et al[31]	0.920	0.643	1.316	−0.456	0.648	
Reck et al[16]	0.610	0.310	1.200	−1.432	0.152	
Scagliotti et al[32]	0.725	0.457	1.149	−1.369	0.171	
Natale et al[33]	0.910	0.457	1.810	−0.269	0.788	
de Boer et al[34]	0.500	0.159	1.576	−1.183	0.237	
Herbst et al[35]	1.160	0.471	2.856	0.323	0.747	
	0.818	0.649	1.030	−1.712	0.087	

Figure 2 Fixed-effects model of hazard ratio (95% CI) of OS associated with therapies with or without AIs.
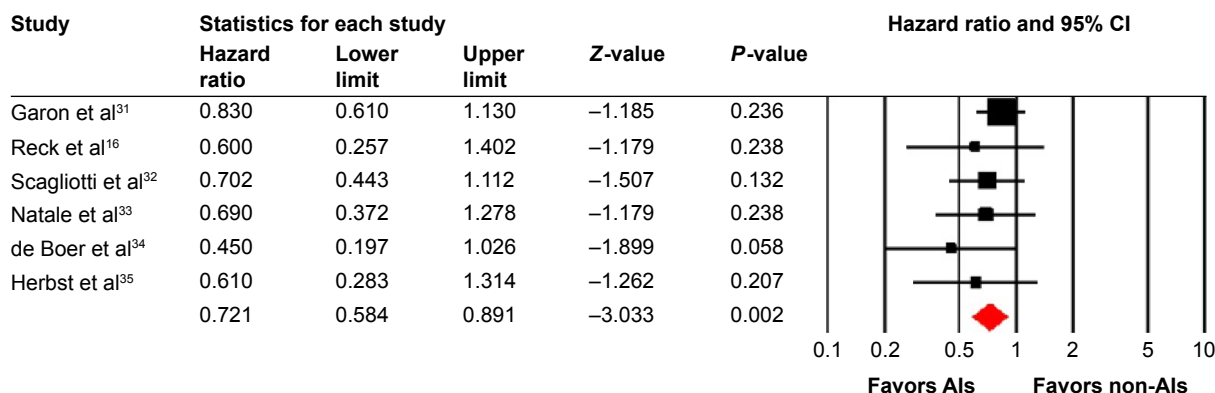**Abbreviations:** CI, confidence interval; OS, overall survival; AIs, angiogenesis inhibitors.

Study	Statistics for each study					Hazard ratio and 95% CI
	Hazard ratio	Lower limit	Upper limit	Z-value	P-value	
Garon et al[31]	0.830	0.610	1.130	−1.185	0.236	
Reck et al[16]	0.600	0.257	1.402	−1.179	0.238	
Scagliotti et al[32]	0.702	0.443	1.112	−1.507	0.132	
Natale et al[33]	0.690	0.372	1.278	−1.179	0.238	
de Boer et al[34]	0.450	0.197	1.026	−1.899	0.058	
Herbst et al[35]	0.610	0.283	1.314	−1.262	0.207	
	0.721	0.584	0.891	−3.033	0.002	

Figure 3 Fixed-effects model of hazard ratio (95% CI) of PFS associated with therapies with or without AIs.
Abbreviations: CI, confidence interval; AIs, angiogenesis inhibitors; PFS, progression-free survival.

Our analysis has some obvious limitations. First, a large number of trials do not report the bevacizumab treatment status. This is largely because these trials are performed to investigate the efficacy of AIs in NSCLC, but not specifically for patients who previously received bevacizumab. Although all of these trials carry out the randomization process adequately, an imbalance of patient characteristics between the two treatment groups of the previously treated bevacizumab subgroup could exist. Therefore, these data should be interpreted cautiously, because the extracted data used for this analysis could not be considered randomized. Second, the published articles provide the crossover rate only for the entire group of enrolled patients without previous bevacizumab treatment subgroup data. Therefore, we could not examine the effect of treatment crossover on the outcomes. Third, the toxicity profile is another important factor for choosing treatment options. However, it is not possible to perform an analysis to deal with such a concern because reports of adverse events from each subgroup are not available. Fourth, although we included all RCTs investigating the efficacy of AIs rechallenge in NSCLC, these is no specific trial to investigate the efficacy of bevacizumab rechallenge in NSCLC patients, who were previously treated with bevacizumab. Thus, the efficacy of bevacizumab rechallenge in the setting remains to be determined. Finally, in the meta-analysis of published studies, publication bias is important because trials with positive results are more likely to be published, while trials with null results tend to be unpublished. Our research detects no publication bias for OS, but not for PFS. With these limitations in mind, a definite conclusion about the usefulness and benefit of AIs rechallenge in the second-line setting cannot be stated. A robust confirmation through a solid Phase III trial is needed before any recommendation can be performed.

Conclusion and future prospective

In conclusion, our study demonstrates that AIs rechallenge is an effective treatment option for patients who were previously exposed to bevacizumab. Further, well-conducted, randomized-controlled biomarker-enriched trials are fundamental to better evaluate this treatment strategy with attention to details such as the toxicities and other accompanying drugs.

Author contributions

QLG and LDZ designed the research; WL, HYZ, and NH conducted the research; LWG and QLG analyzed data; QLG wrote the draft; all authors read, reviewed, and approved the final paper. QLG had primary responsibility for final content. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the paper. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.

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