Original Article

Does the age affect the efficacy of anti-VEGF agents in advanced non-small-cell lung cancer? A meta-analysis

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Abstract: Purpose: This meta-analysis aimed to assess whether the age would affect the efficacy of anti-vascular endothelial growth factor (VEGF) agents in advanced non-small-cell lung cancer (NSCLC). Methods: Electronic databases, including PubMed, Web of Science and the Cochrane Central Register of Controlled trials were searched to identify relevant studies. Eligible studies included prospective randomized controlled trials (RCTs) evaluating therapies with or without anti-VEGF agents in elderly patients with advanced NSCLC. Hazard ratios (HRs) were used to estimate overall survival (OS) and progression-free survival (PFS). Sub-group analysis and publication bias were also evaluated. Results: Ten trials involving a total of 3,163 elderly patients with advanced NSCLC were included. The addition of anti-VEGF agents to therapies in elderly patients significantly improve PFS (HR 0.88, 95% CI: 0.88-1.00, P=0.048), but not for OS (HR 0.99, 95% CI: 0.90-1.10, P=0.91) when compared to controls. On subgroup analysis, similar results were found based on treatment line. No publication bias was detected by Begg’s and Egger’s tests for OS. Conclusions: Among elderly patients with advanced NSCLC, the use of anti-VEGF agents offers an improved PFS, but not for overall survival benefit. With present evidence, we are still unable to clearly set the role of anti-VEGF agents in the treatment of advanced NSCLC in this setting.

Keywords: Non-small-cell lung cancer, elderly, efficacy, anti-VEGF agents, meta-analysis

Introduction

Lung cancer is a leading cause of cancer-related mortality accounting for almost 1.4 million deaths annually, worldwide [1]. Approximately eighty-five percent of all cases of lung cancer have non-small cell lung cancer (NSCLC). The data of Surveillance Epidemiology and End Results (SEER) showed that approximately 53% of lung cancer cases were older than 70 years, and approximately 15% of cases are diagnosed in patients aged more than 80 years [2]. Therefore, the elderly represent a large subgroup of patients affected by advanced NSCLC in our clinical practice. However, there are many challenges involved in the treatment of an elderly population with advanced NSCLC. Old age is commonly associated with several comorbidities, decreased organ function and functional status, which lead to limited life expectancy and reduced tolerance of cancer treatments [3]. Undertreatment is an additional risk for older individuals. Only 35% of patients with regional disease and 27% with metastatic disease received guideline-recommended treatment among patients aged ≥65 years [4]. Furthermore, elderly patients are underrepresented in clinical trials, and treatment decisions are based on results of trials conducted in younger individuals [5-7]. Therefore, the optimal treatment for NSCLC in elderly patients remains undetermined.

During the past decades, the emergence of molecularly targeted agents has provided another strategy for the treatment of elderly patients with advanced NSCLC [8-10], and anti-angiogenesis therapies represent the most promising therapeutic approach being developed [11-14]. Until now, two anti-angiogenesis agents by through inhibiting VEGF signal pathway bevacizumab and nintedanib has been approved for the treatment of advanced NSCLC patients [15, 16]. Nonetheless, there is limited
data regarding the role of anti-VEGF agents in NSCLC patients aged ≥65 years old, whether anti-VEGF agents would benefit elderly patients with advanced NSCLC remains unknown. Thus, we conduct this meta-analysis of all available randomized controlled trials (RCTs) to determine the overall efficacy of anti-VEGF agents in this sub-group patient.

**Material and methods**

**Literature search and inclusion criteria**

The Pubmed, Embase, and Cochrane Library electronic databases were search to identify relevant studies of anti-VEGF agents in advanced non-small-cell lung cancer (published before December 31, 2015). The following search terms were used: “bevacizumab”, “afibbercept”, “anti-VEGF agents”, “sorafenib”, “sunitinib”, “sutent”, “vandetanib”, “axitinib”, “paclitaxel”, “regorafenib”, “apatinib”, “ramucirumab”, “nintedanib”, “angiogenesis inhibitors”, “clinical trials”, “lung cancer”, and “lung neoplasm”. The search was limited to human studies and randomized controlled trials (RCTs). No language restriction was imposed. 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 Jan 2004 and Jun 2015.

**Data extraction and clinical end point**

Two authors independently extracted the following data according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [17] and any discrepancy between the reviewers was resolved by consensus. For each study, the following data was extracted: first author, year of publication, trial phase, the number of elderly patients, treatment regimen, primary endpoints, and median follow-up. A standardized Excel file was used for data extraction. 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 [18]. The quality scale ranges from 0 to 5 points. A higher score indicates better quality. Articles with more than 3 points were considered to have high quality.

**Data analysis**

We assessed the overall efficacy of adding anti-VEGF agents to therapies in the treatment of elderly patients with advanced NSCLC based on data from the included trials. PFS and OS were treated as time-to-event variables, and thus were expressed as hazard ratios (HRs) with 95% CIs for each study. Between-study heterogeneity was estimated using the
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χ²-based Q statistic [19]. The 𝐼² statistic was also calculated to evaluate the extent of variability attributable to statistical heterogeneity between trials.

𝐼² values of 25%, approximately 50%, approximately 75%, and approximately 100% indicated no, low, moderate, and high heterogeneity, respectively. A fixed-effects model (Mantel-Haenszel method) was used, whereas a random effects model (DerSimonian-Laird method) [20] was used when significant heterogeneity existed (𝐼²>50%). A sub-group analysis was conducted according to treatment line. The presence of publication bias was evaluated by using the Beggs and Egger tests [21]. All 𝑝-values were two-sided. All CIs had a two-sided probability coverage of 95%. Statistical analysis was calculated using Version 2 of the Comprehensive MetaAnalysis program (Biostat, Englewood, NJ).

Results

Identification of eligible trials

The initial search of the Pubmed, Embase, and Cochrane Library electronic databases yielded a total of 330 potentially relevant studies. Of these, 30 were excluded for duplicate records, and 280 were excluded after reviewing the title or abstract, leaving 30 articles for full-text review. In the review, 20 trials were excluded for the following reasons shown in Figure 1. Finally, ten published RCTs with sub-group analysis assessing the efficacy of anti-VEGF agents in elderly patients were included [16, 22-30]. The main characteristics of the ten trials were presented in Table 1. A total of 3,709 patients were available for the meta-analysis. Seven trials were performed in first-line settings, and four in second-line. The quality of each included study was roughly assessed according to Jadad scale, the median Jadad score of the included studies was 5 (rang: 3-5).

Overall survival

Seven trials reported OS data of elderly patients. Since between study heterogeneity was not observed, a fixed-effect model was used for OS (𝐼²=0%, 𝑝=0.95). No significant differences were observed with respect to OS (HR 0.99, 95% CI: 0.90-1.10, 𝑝=0.91, Figure 2) between the anti-VEGF agents and controls. We then performed sub-group analysis according to treatment line, and found that the use of anti-VEGF agents as first-line (HR 0.95, 95% CI: 0.89-1.05, 𝑝=0.86, Figure 3) and second-line (HR 0.93, 95% CI: 0.79-1.09, 𝑝=0.31, Figure 4) was associated with a similar benefit in terms of OS.

Table 1. Clinical characteristic of included trials for analysis

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Phase</th>
<th>Line of treatment</th>
<th>No. of elderly patients</th>
<th>Age</th>
<th>Treatment regimes</th>
<th>Median follow-up (m)</th>
<th>Jadad score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garon E.B. et al/2014</td>
<td>III</td>
<td>Second-line</td>
<td>455</td>
<td>≥70</td>
<td>Ramucirumab 10 mg/kg+DOC</td>
<td>9.5</td>
<td>5</td>
</tr>
<tr>
<td>Gridelli C. et al/2014</td>
<td>II</td>
<td>First-line</td>
<td>124</td>
<td>≥70</td>
<td>Vandetanib 100 mg qd po+Gem</td>
<td>NR</td>
<td>5</td>
</tr>
<tr>
<td>Doebele R.C. et al/2014</td>
<td>II</td>
<td>First-line</td>
<td>68</td>
<td>≥65</td>
<td>Ramucirumab 10 mg/kg+Pemetrexed</td>
<td>NR</td>
<td>3</td>
</tr>
<tr>
<td>Scagliotti G.V. et al/2012</td>
<td>III</td>
<td>Second-line</td>
<td>354</td>
<td>≥65</td>
<td>Sunitinib 37.5 mg qd po+erlotinib</td>
<td>21.3</td>
<td>5</td>
</tr>
<tr>
<td>Scagliotti G.V. et al/2012</td>
<td>III</td>
<td>First-line</td>
<td>370</td>
<td>≥65</td>
<td>Motesanib 125 mg qd po+PTX+CBP</td>
<td>NR</td>
<td>5</td>
</tr>
<tr>
<td>Herbst R.S. et al/2011</td>
<td>III</td>
<td>Second-line</td>
<td>327</td>
<td>≥65</td>
<td>Bev 15 mg/kg+erlotinib</td>
<td>19</td>
<td>5</td>
</tr>
<tr>
<td>Scagligotti G. et al/2010</td>
<td>III</td>
<td>First-line</td>
<td>381</td>
<td>≥65</td>
<td>Sorafenib 400 mg bid po+CBP+PTX</td>
<td>NR</td>
<td>3</td>
</tr>
<tr>
<td>Reck M et al/2009</td>
<td>III</td>
<td>First-line</td>
<td>304</td>
<td>≥65</td>
<td>Bev 7.5 mg/kg+DDP+Gem</td>
<td>NR</td>
<td>5</td>
</tr>
<tr>
<td>Sandler A. et al/2006</td>
<td>III</td>
<td>First-line</td>
<td>366</td>
<td>≥65</td>
<td>Bev 15 mg/kg+CBP+PTX</td>
<td>19</td>
<td>3</td>
</tr>
</tbody>
</table>

Abbreviations: DOC, Docetaxel; Gem, Gemcitabine; PTX, Paclitaxel; CBP, Carboplatin; RT, Radiotherapy; Bev, Bevacizumab; DDP, Cisplatin; NR, Not reported.
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Progression-free survival

Six trials with seven comparisons reported PFS data. The pooled hazard ratio for PFS demonstrated that anti-VEGF agents significantly improve PFS giving HR 0.88 (95% CI: 0.88-1.00, P=0.05, Figure 3), compared with controls. There was moderate heterogeneity between trials (I²=46.32%, P=0.083), and the pooled HR for PFS was performed by using random-effects model. A sub-group analysis was performed on the treatment line and found that anti-VEGF agents as first-line (HR 0.98, 95% CI: 0.94-1.02, P=0.33) or second-line therapies (HR 0.90, 95% CI: 0.77-1.06, P=0.20) had a tendency to improve PFS in elderly patients with advanced NSCLC.

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=0.88 for OS and P=0.07 for PFS, respectively). Then, Egger’s test still did not suggest any evidence of publication bias for OS (P=0.99) but not for PFS (P=0.008). The difference in the results obtained from the two methods may be due to a greater statistical power of the regression methods [31].

Discussion

The angiogenesis pathways, playing a critical role in the growth and metastasis of tumors, have been targeted as a promising therapeutic options in NSCLC [9]. The results from latest investigations have showed that the addition of

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Figure 2. Fixed-effects Model of Hazard Ratio (95% CI) of OS Associated with therapies with or without anti-VEGF agents.

Figure 3. Random-effects Model of Hazard Ratio (95% CI) of PFS Associated with therapies with or without anti-VEGF agents.
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angio genesis inhibitors to therapies in advanced NSCLC significantly improve PFS and OS [13, 14]. However, the elderly patients with advanced NSCLC are traditionally underrepresented in clinical trials. The median age across treatment arms in recent major phase III trials was 59 to 63 years, which is considerably younger than the median age of 71 years at diagnosis [6]. Therefore, the applicability of these data to the overall patient population deserves critical appraisal in the absence of trials dedicated specifically to the elderly. Pre-planned and unplanned subset analysis of registration trial data is becoming increasingly common as a substitute measure to provide valuable information to guide the use of targeted agents in the elderly.

Our study includes a total of 3,136 patients from 10 randomized controlled trials. According to the current results, regimens containing anti-VEGF agents have substantial improvements for PFS outcomes in elderly patients when compared to controls (P=0.048). In contrast, benefits in OS is not statistically significant. Similar results were also observed in sub-group analysis according to treatment line. Based on our results, we could conclude that the addition of anti-VEGF agents to treatment therapies could improve PFS in unselected elderly patients with advanced NSCLC, but it does not translate into survival benefit. However, the administration of targeted agents in unselected patients with precisely confirmed targets is not reasonable. Thus, further studies are still needed to identify patients who will most likely benefit from specific anti-angiogenesis therapy. Additionally, we still could not clearly set the role of each anti-angiogenesis agent in the treatment of elderly patients with advanced NSCLC due to limited RCTs included for analysis.

The present meta-analysis has several limitations needed to be considered. First, this analysis is based on published data; and individual patient information is not available. Therefore, confounding variables at patient level, such as comorbidities and prior exposure to treatment therapies, could not be incorporated into the analysis. Second, we include patients treated with different anti-angiogenesis agents. While each of these molecules inhibits VEGF signal pathway, these drugs have different potencies, and have inhibitory properties against a range of non-overlapping targeted receptors. Given the limited sample size of patients treated with any single anti-VEGF agents, we decide to include patients treated with all of these drugs in this class with adequate data on survival of elderly patients with NSCLC, which would increase the clinical heterogeneity among included trials. Furthermore, our study could not answer that which anti-VEGF agent would be the best choice. Finally, in the meta-analysis of published studies, publication bias is important because trials with positive results are more likely to be published. The present study detects no publication bias using Beg and Egger tests for OS but not for PFS.

Conclusion

In conclusion, therapies containing anti-VEGF agents is superior to those without these agents in terms of PFS in unselected elderly patients with advanced NSCLC. However, no significant survival benefit is observed. Further studies are recommended to identify patients who could derive greater benefits from specific anti-VEGF agents.

Disclosure of conflict of interest

None.

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