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The addition of anti-angiogenic tyrosine kinase inhibitors to chemotherapy for patients with advanced non-small-cell lung cancers: A meta-analysis of randomized trials

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Abstract

Objectives—The role of anti-angiogenic tyrosine kinase inhibitors (AATKI) for patients with non-small-cell lung cancers (NSCLC) is uncertain. We conducted a comprehensive meta-analysis to assess the overall utility of adding AATKI to chemotherapy.

Materials and Methods—We included 15 randomized controlled trials (RCTs) of AATKI plus chemotherapy versus chemotherapy involving 7997 patients with advanced NSCLC. Meta-analysis was performed to obtain pooled hazard ratios (HR) for OS and PFS, and pooled odds ratios (OR) for objective response rate (ORR) and grade 3 or greater toxicity. Pre-specified subgroup analyses were performed according to line of chemotherapy, chemotherapeutic regimen and histology.

Results—The addition of AATKI to chemotherapy significantly increased progression-free survival (PFS) (HR 0.83, 95% CI 0.79, 0.87; $P < 0.00001$) and ORR [OR 1.63, 95% CI 1.45, 1.84; $P < 0.00001$], but not overall survival (OS) (HR 0.96, 95% CI 0.91, 1.01; $P = 0.14$). OS benefit was seen in the subset of patients with adenocarcinomas (HR 0.86; 95% CI 0.79, 0.95; $P = 0.002$), especially in the second line setting (HR 0.85; 95% CI 0.76, 0.96; $P = 0.008$). However, both grade

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Conflict of Interest Statement

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3 toxicity (HR 2.08, 95% CI 1.59, 2.73; $P < 0.00001$) and treatment-related deaths (OR 2.37, 95% CI 1.58, 3.56; $P < 0.0001$) were significantly higher with the addition of AATKI.

Conclusion—The addition of AATKI to chemotherapy in patients with advanced NSCLC significantly increased PFS and ORR but not OS, and did so at the expense of increased toxicity and treatment-related deaths. Preclinical and translational research in predictive biomarkers are essential for the clinical development of this class of drugs.

Keywords

Angiogenesis; tyrosine kinase inhibitors; lung cancer; meta-analysis

1. Introduction

Anti-angiogenesis as a form of cancer therapy has held great promise since the original proposal by Folkman in 1971 [1]. A primary driver of tumor-associated angiogenesis is vascular endothelial growth factor (VEGF). VEGF is produced and secreted by tumor cells in response to hypoxia, and binds to a particularly important cognate receptor, VEGF Receptor 2 (VEGFR2) on endothelial cells, promoting proliferation of those cells and initiating a program of angiogenic growth leading to increased tumor vascularity, supplying solid tumors with glucose, oxygen, and other nutrients required for cancer cell survival and proliferation.

The VEGF:VEGFR2 angiogenic axis has been a focus of intense drug development in oncology over the past 20 years. Almost all agents fall into two general classes: (1) highly specific monoclonal antibodies directed against either the ligand (VEGF) or its receptors (VEGFR) and (2) small molecule tyrosine kinase inhibitors of the kinase domain of the VEGFR. Primary examples of the first class of monoclonal antibodies include bevacizumab, an anti-VEGF antibody, and ramucirumab, an anti-VEGFR2 antibody. Both of these agents have been approved for use in non-small cell lung cancer (NSCLC) patients, with bevacizumab use limited to non-squamous NSCLC due to toxicity concerns including deaths from hemoptysis observed in early phase trials including patients with large, centrally located squamous cell cancers [2]. Ramucirumab is approved in combination with docetaxel for recurrent NSCLC. Both agents have been approved by the U.S. FDA based on studies that have shown modest but statistically significant improvements in overall survival (OS) when combined with chemotherapy, relative to chemotherapy alone [3,4].

The remarkable early responses observed using molecularly targeted tyrosine kinase inhibitors prompted substantial excitement surrounding the development of multi-target oral anti-angiogenic tyrosine kinase inhibitors (AATKI) directed against VEGFR2, as a potentially more effective means of inhibiting this key signaling axis than the monoclonal antibodies [5–7]. This excitement has driven development of a large family of anti-VEGFR2 AATKIs, many of which are structurally closely related, and has led to a multitude of clinical trials over the past decade. However, despite the heavy investment from industry, academia and patients, the role of this class of agents in patients with NSCLC remains uncertain.

Earlier meta-analyses have included patients with NSCLC treated with monoclonal antibodies and AATKI, and have attempted to merge datasets involving various combinations with standard agents as well as anti-angiogenic agents given alone [8–10]. Subgroup analyses suggested potential survival benefit when combining anti-angiogenic agents with chemotherapy in the second line setting, with conflicting data on efficacy according to histology and limited information on toxicity [9,10]. In order to clearly inform the clinical development of AATKI as a class of agents for patients with NSCLC, we performed a meta-analysis of randomized controlled trials (RCT) to assess the efficacy and toxicity of adding AATKI to chemotherapy, with preplanned analyses of OS according to histology and chemotherapy partner.

2. Materials and Methods

2.1. Search strategy

In September 2015, we completed a search of PubMed, Medline, EMBASE, Cochrane Library as well as the ASCO, ESMO and WCLC electronic databases for RCT comparing the addition of AATKI to chemotherapy versus chemotherapy alone or plus placebo. Search terms were the combination of “NSCLC” with any of “angiogenesis inhibitors”, “protein kinase inhibitors”, “tyrosine kinase inhibitors”, “axitinib”, “cediranib”, “vandetanib”, “sorafenib”, “linifanib”, “sunitinib”, “motesanib”, “nintedanib” or “vascular endothelial growth factor”. References of included studies and reviews were checked manually. No language restriction was applied.

2.2. Eligibility criteria

Studies that met all of the following criteria were included in this meta-analysis: 1) adult patients with stage IIIB/IV NSCLC; 2) RCT comparing AATKI plus chemotherapy vs chemotherapy alone or chemotherapy plus placebo as the control group; 3) studies using OS as an endpoint with survival analysis reporting hazard ratios. In cases of multiple reports of a single trial, we have included only the latest reports. AATKI was defined as oral tyrosine kinase inhibitors with a putative mechanism of action including targeted inhibition of VEGFR2.

2.3. Study endpoints

The primary endpoint was OS. Secondary endpoints included progression-free survival (PFS), objective response rate (ORR) according to RECIST, grade 3 or greater adverse events according to National Cancer Institute Common Terminology Criteria for Adverse Events (G 3CTCAE). Exploratory endpoints include hypertension, hemorrhage, treatment-related deaths and total on-treatment deaths (G5 AE). Preplanned subgroup analyses of OS were conducted according to line of therapy, histology and chemotherapy partner.

2.4. Quality assessment and data extraction

Two investigators (BTL, TAB) independently extracted abstracts and full text articles based on eligibility criteria. Each study was evaluated for quality assessment based on the Cochrane Collaboration guidelines and “Risk of bias” tool [11]. Any discrepancies were discussed with a third investigator (NP) and resolved by consensus.

2.5. Statistical analysis

The experimental arm was defined as AATKI plus chemotherapy. The control arm was chemotherapy alone or chemotherapy plus placebo. Pooled hazard ratios with 95% confidence intervals (CI) using the generic inverse variance method were calculated for OS and PFS. Pooled odds ratios (OR) with 95% CI using the Mantel-Haenszel method were calculated for ORR and toxicity outcomes (G 3CTCAE, G 3 hypertension, treatment-related deaths and G5 AE). $P < 0.05$ was considered statistically significant. Consistent with reporting of included RCTs, OS and PFS were studied in the intention-to-treat population, ORR was studied in the assessable population, and toxicity outcomes were studied in the at risk population. Heterogeneity across studies was assessed with the Cochran's Q (χ^2) and I^2 statistics. A fixed-effect model was applied unless there is evidence of significant heterogeneity ($I^2 \geq 50\%$), for which a random-effect model was applied. Calculations were performed using the Cochrane Review Manager Version 5.3.

3. Results

3.1. Included studies

A total of 517 articles were reviewed and 15 RCTs involving 7997 patients met eligibility criteria (Fig. 1). Eight AATKI agents (axitinib, cediranib, vandetanib, sorafenib, linifanib, sunitinib, motesanib, nintedanib) were studied in 8 phase II and 7 phase III trials (Table 1) [12–26]. Nine trials were conducted in the first line setting involving the addition of AATKI to platinum doublet chemotherapy and 6 trials were conducted in second line involving the addition of AATKI to pemetrexed or docetaxel. Fourteen trials had final results in journal publications and one trial, the LUME-Lung 2, had results presented and published in abstract form [22]. Seven studies included survival data according to histologic subtypes, with all seven studies specifying squamous histology [15,19–21,23,24,26,27], and four studies specifying adenocarcinoma histology [20,21,24,26]. Toxicity reporting was heterogeneous, with 9 studies reporting G 3CTCAE, 12 studies reporting G 3 hypertension, 10 studies reporting treatment-related deaths, and 3 more studies reporting G5 AE without causal attribution. The two studies by Heymach et al., 2007 [25] and Ramalingam et al., 2015 [18] included two different doses of AATKI, and both comparisons with chemotherapy control were included in the meta-analysis. The study by Heist et al., 2014 [23] included three arms, but only the two arms comparing AATKI plus chemotherapy vs chemotherapy control was included in this meta-analysis. The study by Belani et al., 2014 [12] included two different dosing schedules of axitinib (continuous versus intermittent), only the continuous schedule arm was included in this analysis.

3.2. Excluded studies

Two phase II randomized trials were excluded due to insufficient survival data required for meta-analysis [28,29]. In these small studies of sorafenib ($n = 100$) [28] and vandetanib ($n = 124$) [29] with chemotherapy, descriptive statistics were used without formal survival analysis reporting hazard ratios.

3.3. Risk of bias

The quality of the included studies were assessed using the Cochrane risk of bias tool [11]. The included trials were generally of good quality with a low risk of bias (Fig. S1). Of the 15 trials included, 6 were deemed to be of excellent quality without evidence of bias. Most common issues encountered were the lack of description of randomization process and allocation concealment (selection bias), and the lack of blinding in the trials by Belani et al. [12], Dy et al. [13], and Heist et al. [23] (performance bias). High risk of bias was identified in the studies by Belani et al. [12] and Ramalingam et al., 2015 [18], with a high proportion of patients discontinuing the study for unexplained reasons (attrition bias).

3.4. Overall survival

In the overall population ($n = 7997$), the addition of AATKI to chemotherapy did not significantly prolong OS (HR 0.96, 95% CI 0.91, 1.01; $P = 0.14$) (Fig. 2). Preplanned subgroup analyses did not show a significant OS benefit in either first line ($n = 3835$) (HR 0.96, 95% CI 0.88, 1.04; $P = 0.30$) or second line setting ($n = 4162$) (HR 0.96, 95% CI 0.90, 1.03; $P = 0.30$). Chemotherapy partner alone did not affect OS, whether combined with a taxane (HR 0.96, 95% CI 0.90, 1.02; $P = 0.17$) or with a non-taxane (HR 0.97, 95% CI 0.88, 1.07; $P = 0.57$) (Fig. S2). Histologic subgroup analysis did reveal that the addition of AATKI to chemotherapy produced a significant OS benefit in the adenocarcinoma subgroup ($n = 2713$) (HR 0.86, 95% CI 0.79, 0.95; $P = 0.002$), in contrast to a lack of benefit seen in the squamous histology subgroup ($n = 1632$) (HR 1.03, 95% CI 0.92, 1.16; $P = 0.59$) (Fig. 3). Subgroup interaction ($I^2 = 82.2\%$ and $P = 0.02$) was also significant here supporting the difference between the two histologic subtypes. The subgroup with the greatest magnitude of OS benefit appeared to be the addition of AATKI to second line chemotherapy in patients with lung adenocarcinomas ($n = 1823$) (HR 0.85, 95% CI 0.76, 0.96; $P = 0.008$) (Fig. S3).

3.5. Progression free survival and objective response rates

In the overall population, the addition of AATKI to chemotherapy significantly prolonged PFS (HR 0.83, 95% CI 0.79, 0.87; $P < 0.00001$) (Fig. S4), and objective response rates (ORR) [Odds Ratio (OR) 1.63, 95% CI 1.45, 1.84; $P < 0.00001$] (Fig. S5).

3.6. Toxicity

Total G₃ CTCAE was significantly higher in the AATKI plus chemotherapy group compared to chemotherapy control group (HR 2.08, 95% CI 1.59, 2.73; $P < 0.00001$) (Fig. S6). G₃ hypertension was also significantly more common in AATKI plus chemotherapy group compared to chemotherapy control (OR 4.36, 95% CI 2.81, 6.77; $P < 0.00001$), consistent with a class effect of AATKI (Fig. S7). Severe hemorrhage reported was numerically higher (58 vs 52) in the AATKI plus chemotherapy group, but due to heterogeneous reporting methods and definitions across studies this could not be subjected to meta-analysis. Treatment-related deaths were significantly higher in the AATKI plus chemotherapy group (76 of 2736, 2.8%) compared to the chemotherapy control group (31 of 2645, 1.2%) (OR 2.37, 95% CI 1.58, 3.56, $P < 0.0001$) (Fig. 4). The increased treatment-related deaths were significant in both first line (OR 4.24, 95% CI 2.00, 9.00, $P = 0.0002$) and second line settings (OR 1.74, 95% CI 1.06, 2.86, $P = 0.03$). When pooling all G₅ AE

data without causal attribution as reported in 13 RCTs, overall on-treatment deaths remain significantly higher in the AATKI plus chemotherapy group (435 of 3876, 11.2%) compared to the chemotherapy control group (312 of 3814, 8.2%) (OR 1.45, 95% CI 1.24, 1.69, $P < 0.00001$) (Fig. S8).

4. Discussion

One theoretical advantage of multi-targeted AATKIs over high-specificity monoclonal antibodies is the ability to inhibit not only tumor angiogenesis, but also closely related receptor tyrosine kinases regulating growth and survival, including the receptors for platelet derived growth factors, fibroblast growth factors and endothelial growth factors [6]. However, after a decade of randomized clinical trials involving close to eight thousand patients, the role of this class of agents for patients with NSCLC remains uncertain. We believe that the data presented here should prompt us to reconsider future development of these agents in the absence of a mechanism-based biomarker strategy to inform patient selection.

The first meta-analysis of AATKI in patients with NSCLC by Xiao et al. [8] included only 6 RCTs evaluating 3 agents, and reported improved PFS and ORR when AATKI was added to chemotherapy. However, a subsequent larger meta-analysis by Liang et al. [9] pooled results from different combinations of AATKI with chemotherapy, other tyrosine kinase inhibitors or as a single agent. In this larger study, an OS benefit was not found in the overall population, although subgroup analyses showed potential benefit when AATKI was added to standard therapy in the second line setting, and possibly in studies including squamous histology [9]. Leading to further controversy in this area, a more recent meta-analysis by Sheng et al. [10] showed improvement in OS when an anti-angiogenic agent was added to chemotherapy for non-squamous histology, but this review included anti-angiogenic monoclonal antibodies. The differences in methodology and heterogeneity in these meta-analyses have prevented any firm conclusions or directions to be drawn regarding the clinical development of AATKI for patients with NSCLC.

Our meta-analysis was conducted building on these previous results which suggested a benefit of AATKI when added to chemotherapy in the second line setting [8–10]. Although the biologic basis for a preferential effect of AATKI based on line of therapy is unknown, the benefit observed when adding AATKI to chemotherapy is consistent with preclinical data supporting the hypothesis that anti-angiogenic agents may normalize tumor vasculature thus improving perfusion, reducing tissue hypoxia and enhancing the outcome of chemotherapy [30]. As we only included randomized trials adding AATKI to chemotherapy, our meta-analysis was relatively homogeneous when pooling survival endpoints ($I^2 = 21\%$ for OS, $I^2 = 11\%$ for PFS). While adding AATKI to chemotherapy significantly increased PFS and ORR, it did not improve OS in the overall population. This lack of OS benefit differed from the meta-analysis by Sheng et al. [10] likely due to the fact that the previous analysis included monoclonal antibodies such as ramucirumab which was recently shown to improve OS [4].

Preplanned subgroup analysis did not find a significant OS benefit by line of treatment or chemotherapy partner. In the overall population, adding AATKI to a taxane chemotherapy partner did not improve OS, contrary to the meta-analysis by Sheng et al. [10] where the positive effect with taxanes again may have been influenced by the positive docetaxel plus ramucirumab study [4]. Our study did find that patients with adenocarcinoma histology had a modest, but statistically significant OS benefit when AATKI was added to chemotherapy (HR 0.86, $P = 0.002$). This OS benefit was most pronounced in studies where nintedanib or vandetanib was added to second line chemotherapy in patients with lung adenocarcinoma. The reason behind the differences in AATKI efficacy by histology is still unknown, but it may reflect the substantial differences in the spectra of genomic alterations in adenocarcinoma vs. squamous cell NSCLC [26,31,32]. However, the lack of comprehensive molecular profiling of tumors in these studies has prevented any informative correlative and translational studies, especially in the exceptional responders to AATKI. For instance, an off target effect of the AATKI vandetanib is inhibiting the rearranged during transfection (RET) transmembrane receptor tyrosine kinase, and vandetanib has been demonstrated to produce clinical responses in patients with *RET* rearranged lung cancers [33,34]. The impact of the off target effects of AATKI in these trials is unknown.

The increased overall toxicity in G 3CTCAE seen in patients who received the addition of AATKI to chemotherapy is a critical area overlooked by previous reviews. While the increase in grade 3 or greater hypertension as a class effect of AATKI is not surprising, the significant increase in treatment-related deaths is concerning. Although the absolute increase in treatment-related deaths was small (2.8% vs 1.2%, $P < 0.0001$), this finding does have important clinical implications. It is notable that the magnitude of increase in treatment-related deaths was greater in the first line setting where AATKI was combined with platinum doublet chemotherapy (OR 4.24, $P = 0.0002$), though this increase was also significant in the second line setting (OR 1.74, $P = 0.03$). When meta-analyzing all grade 5 toxicity data including patients who died during treatment due to lung cancer, the number of on-treatment deaths remained significantly higher in the AATKI group (11.2% vs 8.2%, $P < 0.00001$).

Nintedanib is the only AATKI that has received regulatory approval by the European Medicines Agency for use in patients with advanced NSCLC in the second line setting in combination with docetaxel [26]. In the current landscape of advanced NSCLC management where second line ramucirumab and immune checkpoint inhibitors have become available to patients across histologies [4,35–37], and bevacizumab remaining as a standard of care in first line for non-squamous NSCLC [3], the clinical development of AATKI has become increasingly problematic in the absence of a biomarker to enrich enrollment. It is worth noting that even in the subgroup where AATKI was found to be most efficacious by this meta-analysis, i.e. when added to second line chemotherapy in adenocarcinoma histology (HR 0.85, $P = 0.008$), the magnitude of benefit is similar to what was seen in the REVEL trial in which ramucirumab was added to docetaxel regardless of NSCLC histology (HR 0.86, $P = 0.023$) [4].

Translational research in predictive biomarkers for AATKI efficacy in patients with NSCLC is essential if these agents are going to be further developed for this indication. We suggest that rigorous preclinical and translational early phase studies for combinations of AATKI

with novel agents, including EGFR targeted agents or immune checkpoint inhibitors, are essential before launching large randomized trials similar to those we have witnessed in the past decade. The need to focus on predictive biomarkers and translational science as concluded from this review will hopefully not only make AATKI a more useful class of drugs, but uncover new insights into the mechanisms of targeting angiogenesis that may fulfill its potential to help many more patients with lung cancers and other solid tumors to a greater magnitude of benefit.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.lungcan.2016.10.004>.

Fig. 1.
Flowchart of search for studies.

Fig. 2.
Forest plot and pooled hazard ratio for overall survival.

Fig. 3.

Forest plot and pooled hazard ratio for overall survival by histology subgroups.

Fig. 4.
Forest plot and pooled odds ratio for treatment-related deaths.

Table 1

Characteristics of included randomized controlled trials.

First Author (Year)	Study Name if available	Number of patients meta-analyzed	Clinical trial phase	AATKI	Chemotherapy	Line of therapy
Belani (2014)		112	2	Axitinib	Cisplatin Pemetrexed	1st
Dy (2013)	NCCCTG N0528	87	2	Cediranib	Carboplatin Gemcitabine	1st
Goss (2010)	NCIC BR24	296	2	Cediranib	Carboplatin Paclitaxel	1st
Heymach (2008)	6474IL/0007	108	2	Vandetanib	Carboplatin Paclitaxel	1st
Laurie (2014)	NCIC BR29	306	2	Cediranib	Carboplatin Paclitaxel	1st
Paz-Ares (2012)	NEXUS	772	3	Sorafenib	Cisplatin Gemcitabine	1st
Ramalingam (2015)		138	2	Linifanib	Carboplatin Paclitaxel	1st
Scagliotti (2010)	ESCAPE	926	3	Sorafenib	Carboplatin Paclitaxel	1st
Scagliotti (2012)	MONET 1	1090	3	Motesanib	Carboplatin Paclitaxel	1st
de Boer (2011)	ZEAL	534	3	Vandetanib	Pemetrexed	2nd
Hanna (2013)	LUME Lung 2	713	3	Nintedanib	Pemetrexed	2nd
Heist (2014)	CALGB 30704 (Alliance)	83	2	Sunitinib	Pemetrexed	2nd
Herbst (2010)	ZODIAC	1391	3	Vandetanib	Docetaxel	2nd
Heymach (2007)	6474IL/0006	127	2	Vandetanib	Docetaxel	2nd
Reck (2014)	LUME Lung 1	1314	3	Nintedanib	Docetaxel	2nd