Angiogenesis, multitarget kinase inhibitors and non-small cell lung cancer: a lesson from MONET1 trial

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Submitted Aug 23, 2012. Accepted for publication Sep 26, 2012.
DOI: 10.3978/j.issn.2218-6751.2012.09.12
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Angiogenesis, the development and formation of new blood vessels, has been described as one of the hallmarks of cancer, playing an important role in tumor growth, invasion and metastasis (1-4). Several signaling pathways are implicated, such as the vascular endothelial growth factor (VEGF) pathway and platelet-derived growth factor (PDGF) pathway (5). Inhibiting tumor angiogenesis is a therapeutic strategy that has been tested in different solid tumors, including non-small cell lung cancer (NSCLC) (6-8).

The main strategy to cause inhibition of the angiogenesis process is by blocking key mediators of the pathway. The combination of antiangiogenic agents with chemotherapy seems to be attractive as theoretically would inhibit both cell proliferation and vascularization.

Bevacizumab is a humanized monoclonal antibody that acts by binding and neutralizing all VEGF-A isoforms (9,10). Two pivotal phase III studies were conducted in patients with recurrent or advanced nonsquamous NSCLC chemotherapy-naïve. In the ECOG4599 trial, 878 patients were assigned to receive chemotherapy with paclitaxel and carboplatin with or without bevacizumab. There was a significant increase in overall survival (OS), the primary end point of the study, from 10.3 months with chemotherapy alone to 12.3 months in the arm with bevacizumab (hazard ratio for death, 0.79; P=0.003) (11). In a second study, the European AVAiL trial, 1,043 patients were randomized to receive cisplatin and gemcitabine plus low-dose bevacizumab (7.5 mg/kg), high-dose bevacizumab (15 mg/kg), or placebo every 3 weeks until disease progression. The trial was not powered to compare the two doses of bevacizumab directly. That study demonstrated a higher response rate (RR) and longer progression-free survival (PFS) time with both doses of bevacizumab, but no statistically significant improvement in OS was observed (12).

Another approach to inhibit angiogenesis is represented by the use of small-molecules that prevent activation of VEGF receptors, thus inhibiting downstream signaling pathways. These tyrosin-kinase inhibitors (TKIs) are able to inhibit different angiogenesis pathways, so they could theoretically offer increased efficacy, but also more toxicity. Several clinical trials are being conducted designed to compare chemotherapy alone with chemotherapy plus different TKIs such as sorafenib, axitinib, sunitinib, vandetanib, cediranib or motesanib (13-22).

Until date, no randomized clinical trial has shown an improvement in survival with the addition of any TKI to doublet-platinum based chemotherapy in the first line metastatic setting. In a phase II trial, vandetanib in combination with carboplatin and paclitaxel led to a higher RR and longer PFS time although no difference in OS when compared with carboplatin and paclitaxel alone in 108 chemotherapy-naïve patients with advanced NSCLC (15). Other phase II/III study, the BR24 trial, randomized 251 patients to receive carboplatin and paclitaxel plus cediranib or placebo showing a higher RR with the addition of the antiangiogenic agent, but no significant improvement in PFS or OS was detected (16). Two phase III trials have been reported to test the role of sorafenib in combination with chemotherapy. The ESCAPE study was designed to show an improvement in OS with the addition of sorafenib to carboplatin and paclitaxel. After 926 patients recruited, the primary endpoint of OS was not met and the study was closed as a result of the detrimental effect of sorafenib on patients with squamous cell carcinoma (17). The NExUS trial included 772 patients and squamous histology was excluded after safety data reported in the ESCAPE trial.

The addition of sorafenib to gemcitabine and cisplatin failed to provide significant benefit in OS but a trend toward a longer PFS was observed (18,19).

Motesanib is an orally administered small agent that inhibits VEGF receptor 1, 2 and 3, PDGFR and cKIT. It is currently in clinical development in different cancer types, including NSCLC (22). In a phase IB study in patients with advanced NSCLC motesanib was administered in combination with paclitaxel and carboplatin and/or panitumumab. Treatment-related adverse events were generally mild to moderate, with fatigue and hypertension being the most common grade 3 adverse events. The maximum dose tolerated (MTD) of the study was 125-mg once daily and it has been considered the dose for subsequent studies (23). In a phase II study the activity of carboplatin and paclitaxel plus motesanib 125 mg once daily (arm A), motesanib 75 mg twice daily for 5 days on/2 days off (arm B) or plus bevacizumab 15 mg/kg every 3 weeks (arm C) was similar (24).

Recently, in *Journal of Clinical Oncology*, Scagliotti *et al*. have reported the results of the phase III trial involving NSCLC patients which compares carboplatin plus paclitaxel alone or in combination with motesanib (MONET1 trial) (25). This randomized, multicenter, double-blind study, was designed to show an improvement in overall survival (OS) with the addition of motesanib 125 mg daily to carboplatin and paclitaxel in the first line setting in patients with advanced NSCLC. After a planned review of data from 600 patients (including 223 with squamous histology), squamous histology was excluded due to a higher early mortality rate and a higher incidence of gross hemoptysis in the arm of motesanib. Finally, a total of 1,090 patients with nonsquamous NSCLC were randomly assigned to receive or not the antiangiogenic agent.

Median OS was not significantly improved with the addition of motesanib to chemotherapy [arm A 13.0 months *vs.* arm B 11.0 months, hazard ratio (HR), 0.90; 95% CI, 0.78 to 1.04; P=0.14]. Although improvements in PFS (arm A 5.6 months *vs.* arm B 5.4 months HR, 0.79; 95% CI, 0.68 to 0.90; P<0.001) and ORR (arm A 40% *vs.* arm B 26%; P<0.001) favouring the motesanib arm were observed, suggesting certain grade of activity for the combination. The toxicity profile showed a significant increase of serious adverse events (AEs) including grade 3, 4 and 5 (arm A 49% *vs.* arm B 34%). Gastrointestinal events, hypertension, pneumonia, cholecystitis, and other gallbladder-related disorders generally occurred more frequently in the motesanib arm and it appeared to have contributed to treatment discontinuation. Based on previous studies which showed significant associations between increasing levels of PLGF during the first 3 weeks of treatment with motesanib and efficacy outcomes, levels of that biomarker were analyzed in the study, but no association between PLGF change and OS was observed (26,27).

Because MONET1 did not reach its primary end point, motesanib is another antiangiogenic agent that has failed to show clinical benefit when added to chemotherapy in advanced NSCLC. To explain the failure of the combining chemotherapy-antiangiogenic therapy there are several reasons. One of the main problems is the lack of predictive markers in antiangiogenic therapy. While EFGR activation mutations have been demonstrated as a predictive marker of response to EGFR TKIs (erlotinib or gefitinib), no biological marker has been validated for prediction of a better response to antiangiogenic therapy. Without a predictive biomarker, it is not possible to conduct a preselection strategy of patients who may benefit or who will develop toxicities with antiangiogenic agents. Furthermore, another important reason for the lack of benefit observed with the addition of antiangiogenic TKIs is that the mechanisms of tumour escape are not well known. Apart from VEGF pathway, there are many other signalling pathways such as angiopoietins (Ang-1 and Ang-2), Notch and integrin pathways, that may provide a source for alternative growth when one pathway is blocked (28). In addition to the lack of survival benefit in NSCLC, antiangiogenic TKIs agents have been associated with significant toxicity. Recent meta-analyses evaluating the adverse effects of sorafenib and sunitinib in different tumour types showed increased risk of bleeding (relative risk, 2.0; P=0.015) (29), arterial thrombotic events (relative risk, 3.03; P=0.015) (30) and treatment-related mortality (relative risk, 2.23; P=0.023) (31), when using these agents.

In conclusion, the repeated lack of efficacy observed with the addition of VEGFR TKIs to first line standard regimens of chemotherapy for NSCLC patients represents a new challenge. The preclinical and biomarkers studies are essential in the identification of a predictive biomarker for the use of these compounds (32). A better knowledge on angiogenesis and potential mechanisms of resistance to antiangiogenic therapies may lead to a new paradigm in which antiangiogenic TKIs can be effectively combined to chemotherapy.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Mendivil AN, Rodriguez PM, Felip E. Angiogenesis, multitarget kinase inhibitors and non-small cell lung cancer: a lesson from MONET1 trial. Transl Lung Cancer Res 2013;2(1):E13-E16. DOI: 10.3978/j.issn.2218-6751.2012.09.12

