Oncology and Translational Medicine
DOI 10.1007/s10330-015-0072-1

April 2015, Vol. 1, No. 2, P58–P64

REVIEW ARTICLE

Antiangiogenic agents combined with chemotherapy in non-small cell lung cancer

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Abstract

As a targeted therapy, antiangiogenic treatment has been increasingly studied for advanced non-small cell lung cancer (NSCLC) and has proven effective for the treatment of advanced NSCLC. Bevacizumab, a monoclonal antibody targeting angiogenesis, is the only antiangiogenic agent approved for use in combination with first-line chemotherapy for non-squamous NSCLC. Small-molecule inhibitors targeting the tyrosine kinase receptor have also shown promise when combined with standard chemotherapeutic agents in patients with advanced NSCLC. However, unlike bevacizumab, not all other antiangiogenic agents show significant benefits when combined with chemotherapy. As for the failures of most other combinations, the combination schedule may be an important reason that has so far been overlooked in clinical trials. This article reviews the combination of angiogenic agents with chemotherapy in the treatment of NSCLC.

Received: 16 Feburary 2015
Revised: 26 February 2015
Accepted: 5 March 2015

Key words: non-small cell lung cancer (NSCLC); antiangiogenic agent; chemotherapy; combination schedule

Lung cancer is one of the leading causes of cancer-related deaths, of which 85% are from non-small cell lung cancer (NSCLC) [1]. Most patients with NSCLC are diagnosed with advanced inoperable disease, and their only choice is systemic chemotherapy (CT). At present, the five-year survival rate for patients treated with standard platinum-based therapy is only 15% since CT provides a modest clinical benefit and patients often discontinue because of the significant toxicity [2]. With the progressive understanding of tumor biology and the identification of promising molecular targets, the management of targeted therapy, including targeting angiogenesis for NSCLC, has evolved considerably in recent years. Bevacizumab, the first antiangiogenic agent approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of NSCLC, has been consistently associated with a significant clinical benefit in advanced non-squamous NSCLC when combined with first-line CT [3]. Unlike bevacizumab, trials of other agents do not always show significant improvements in overall survival (OS) when combined with CT. Possible reasons for the failures of these clinical trials include the combination schedule and the lack of predictive biomarkers for increased sensitivity to these drugs in patients. In this article, we briefly review the role of angiogenesis in tumor growth and as a therapeutic target, and then summarize several agents that are either in use or under development for the treatment of patients with NSCLC. Finally, we emphasize the challenges and outlook for antiangiogenic agents when combined with CT in NSCLC treatment.

Angiogenesis in tumorigenesis and the possible rationale for the synergy between angiogenesis inhibitors and CT

In 1971, Dr. Judah Folkman first postulated the hypothesis that angiogenesis is a crucial regulator of the growth, invasion, and metastasis of human malignancies, including lung cancer [4–5]. When a tumor grows to larger than 2 mm in diameter, it cannot acquire sufficient nutrients and oxygen from existing blood vessels, and changes therefore occur in the tumor microenvironment, stimulating the release of angiogenic factors from tumor cells and other stromal cells. The "angiogenic switch" is then activated owing to an imbalance between pro-angiogenic and anti-angiogenic factors [6]. Subsequently, vessels be-

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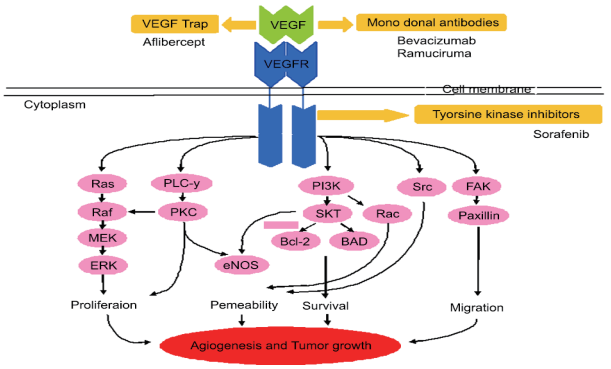

Fig. 1 Signal transduction process for VEGF/VEGFR and various therapeutic strategies to inhibit VEGF signaling. VEGF (green parts) binding to VEGFR promotes receptor dimerization and autophosphorylation (blue parts). After receptor activation, multiple intracellular signaling cascades are initiated, mediated by several downstream effectors (pink ovals). The activation of the downstream signal transduction molecules leads to several different endothelial cell functions, such as migration, vascular permeability, survival, and proliferation, which are required for angiogenesis and tumor growth (red parts). VEGF signaling can be inhibited by impairing the extracellular components of the pathway with antibodies or biologics that target VEGF and VEGFR. VEGFR intracellular kinase activity can be blocked by various small-molecule tyrosine kinase inhibitors. BAD, Bcl-2-associated death promoter; Bcl-2, B-cell lymphoma protein 2; eNOS, endothelial nitric oxide synthase; ERK, extracellular signal-regulated kinase; FAK, focal adhesion kinase; MEK, mitogen-activated protein kinase/extracellular signal-regulated kinase kinase; PI3K, phosphatidylinositol 3-kinase; PKC, protein kinase C; PLC, phospholipase C; Ras, rat sarcoma; Raf, rapidly accelerated fibrosarcomamatibodies or biologics that target VEGF and VEGFR. VEGFR intracellular kinase activity can be blocked by various small-molecule tyrosine kinase inhibitors. BAD, Bcl-2-associated death promoter; Bcl-2, B-cell lymphoma protein 2; eNOS, endothelial nitric oxide synthase; ERK, extracellular signal-regulated kinase; FAK, focal adhesion kinase; MEK, mitogen-activated protein kinase/extracellular signal-regulated kinase kinase; PI3K, phosphatidylinositol 3-kinase; PKC, protein kinase C; PLC, phospholipase C; Ras, rat sarcoma; Raf, rapidly accelerated fibrosarcoma

come dilated, tortuous, and more permeable, leading to blood vessel sprouting and the proliferation of vascular endothelial cells. This uncontrolled angiogenesis leads to tumor growth and the formation of metastases. Angiogenesis is a complex process regulated by cellular cues, multiple receptor-mediated signaling networks, and a number of pro- and anti-angiogenic factors, of which vascular endothelial growth factor (VEGF) is the most potent and well-studied pro-angiogenic signaling pathway, and also platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF) [5]. Most of these signaling pathways are initiated by activated receptor tyrosine kinases (RTKs) [7]. RTKs such as vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and fibroblast growth factor receptor (FGFR), are expressed in malignant tissues and act in concert, playing diverse and major roles in angiogenesis, tumor growth, and metastasis [8]. After binding ligands, for example, VEGF, PDGF, and FGF, RTKs undergo dimerization and autophosphorylation of several tyrosine residues at the kinase domain and the C-terminal tail, activating downstream signaling pathways, including phosphoinositide-3 kinase (PI3K) and phospholipase Cγ, which are involved in endothelial cell survival, permeability, proliferation, and migration [9]. The combined effects result in angiogenesis and tumor development (Fig.1).

Tumor blood vessels also have abnormal structural arrangements, as stated above. These neo-angiogenic vessels are often poorly perfused with low microvascular pressure, thus promoting blood stasis and hypoxia, both of which are inducers of the release of pro-angiogenic factors. This can lead to suboptimal delivery of CT and increased resistance in tumors. Antiangiogenic agents, in addition to inhibiting the growth of tumor vasculature, are believed to transiently normalize the tumor vascular supply, resulting in improved chemotherapeutic drug delivery [10–12]. Since their toxicity does not overlap with that of CT agents, antiangiogenic agents have been combined with a variety of CT agents for the treatment of patients with NSCLC [13].

Some common antiangiogenic agents that have been combined with CT are: (1) high-molecular-weight monoclonal antibodies that target the VEGF signaling pathway (bevacizumab and ramucirumab) or VEGF Trap (aflibercept); (2) small-molecule, orally administered tyrosine kinase inhibitors (TKIs) that directly inhibit tyrosine kinase receptors (sorafenib); (3) vascular disrupting agents (VDAs; vadimezan), compounds that are designed to prevent tumor development by destroying existing tumor vasculature; and (4) agents targeting vascular endothelial cells (endostar).

Antiangiogenic agents in combination with CT in NSCLC

Targeting the VEGF pathway

Monoclonal antibodies

Bevacizumab (Avastin), a recombinant humanized monoclonal antibody targeting VEGF, prevents the interaction between VEGF and its receptors by binding soluble VEGF, thus neutralizing its biological activity [5]. Bevacizumab is the only antiangiogenic agent currently approved by the FDA and the EMA for the treatment of NSCLC, based on the results of two classical Phase III studies, the Eastern Cooperative Oncology Group 4599 (ECOG4599) trial and the Avastin in Lung Cancer (AVAiL) trial, in 2006 and 2009, respectively [14–15]. These two trials are restricted to patients with tumors with non-squamous histology because of a previous Phase II trial. One trial examined carboplatin and paclitaxel with

or without bevacizumab in 99 patients with advanced or recurrent NSCLC, showing the association of bleeding with squamous histology [16]. The Phase III ECOG4599 trial evaluated carboplatin/paclitaxel with or without bevacizumab (15 mg/kg) in 878 CT-naïve patients with non-squamous NSCLC. In this trial, bevacizumab was associated with significant prolongation of both OS [12.3 months vs 10.3 months; hazard ratio (HR) for death: 0.79; $P = 0.003$] and progression-free survival (PFS; 6.2 months vs 4.5 months, HR 0.66; $P < 0.001$) vs placebo, illustrating the benefit of bevacizumab in combination with CT as a first-line treatment for patients with advanced non-squamous NSCLC [14]. In the AVAiL trial, 1043 patients with non-squamous NSCLC were randomized to receive cisplatin/gemcitabine with or without bevacizumab (7.5 or 15 mg/kg). As with ECOG4599, bevacizumab was associated with an improvement in PFS (at both doses) vs placebo, but there was no significant improvement in OS with bevacizumab. Interestingly, improved PFS was observed in elderly patients in the AVAiL trial, unlike in the ECOG4599 trial. Toxicities that are often associated with bevacizumab include neutropenia, febrile neutropenia, bleeding events, hypertension, and proteinuria [15]. Recently, a randomized Phase III trial, focusing on maintenance bevacizumab–pemetrexed after first-line cisplatin–pemetrexed–bevacizumab for advanced non-squamous NSCLC, suggested increments in both PFS and OS in the maintenance with bevacizumab–pemetrexed group, and the combination was well tolerated. In this trial, 253 patients were randomized to maintenance treatment with bevacizumab ($n = 125$) or bevacizumab–pemetrexed ($n = 128$). At a median follow-up of 14.8 months, patients allocated to bevacizumab–pemetrexed had significantly improved PFS vs those on bevacizumab when measured from randomization [7.4 vs 3.7 months, HR 0.57, 95% confidence interval (CI) 0.44–0.75; $P < 0.0001$]. OS events occurred in 58% of patients. OS was numerically longer with bevacizumab–pemetrexed vs bevacizumab when measured from randomization [17.1 vs 13.2 months, HR 0.87 (0.63–1.21); $P = 0.29$]. Second-line therapy was administered to 77% and 70% of patients in the bevacizumab and bevacizumab–pemetrexed arms, respectively. No new adverse events were reported during this updated analysis [17].

Ramucirumab (RAM) is another monoclonal antibody that specifically binds VEGFR2 and blocks ligand binding and activation [18]. A Phase II study evaluating RAM as a first-line NSCLC therapy in combination with carboplatin/paclitaxel resulted in a 6-month PFS rate and a safety profile comparable with the historical control [19]. Another randomized Phase II study evaluated the administration of RAM in combination with first-line platinum-based CT in 140 patients with non-squamous advanced NSCLC. Patients were randomized to receive a maximum of six cycles of either cisplatin or carboplatin and pemetrexed every 3 weeks followed by maintenance treatment with pemetrexed (arm A), or RAM in combination with either cisplatin or carboplatin and pemetrexed every 3 weeks followed by maintenance treatment with RAM and pemetrexed (arm B). According to the data analysis, the median PFS was 5.6 months for arm A and 7.2 months for arm B (HR 0.75; $P = 0.132$). The objective response rates (ORR) were 38.0% and 49.3% for arm A and arm B, respectively ($P = 0.180$). The disease control rate (DCR) was 70.4% for arm A and 85.5% for arm B ($P = 0.032$). The grade 3 or higher adverse events occurring in 10% or more of patients were thrombocytopenia, neutropenia, fatigue, anemia, nausea, back pain, and hypertension [20]. RAM plus docetaxel vs placebo plus docetaxel for second-line treatment of Stage IV NSCLC after disease progression on platinum-based therapy is a multicentre, double blind, randomized Phase III trial. It suggested that RAM plus docetaxel improves survival when used as a second-line treatment in patients with Stage IV NSCLC. Median overall survival was 10.5 months for 628 patients receiving RAM plus docetaxel and 9.1 months for 625 patients who received placebo plus docetaxel (HR 0.86, $P = 0.023$). Median PFS was 4.5 months for the RAM group compared with 3.0 months for the control group ($P < 0.0001$). Toxicities were manageable with appropriate dose reductions and supportive care [21]. While RAM monotherapy is approved by the FDA as a second-line treatment for advanced or metastatic gastric cancer and gastroesophageal junction carcinoma (April 2014), its role for advanced NSCLC is still being debated.

VEGF Trap

Aflibercept is a recombinant protein that is designed to act as a soluble decoy receptor for VEGF-A, VEGF-B, and PLGF, thus preventing them from binding to their endogenous receptors. Therefore, it acts as an inhibitor of tumor angiogenesis and metastasis [22–23]. A Phase III trial assessing aflibercept plus docetaxel vs docetaxel alone in 913 patients with advanced NSCLC, which had progressed following first-line CT, demonstrated that aflibercept could improve median PFS (5.2 vs 4.1 months; HR 0.82; $P = 0.0035$). However, the addition of aflibercept to standard docetaxel therapy did not improve OS. Major toxicities that were more frequent in the aflibercept arm included stomatitis, neutropenia, hemorrhage, hypertension, epistaxis, dysphonia, proteinuria, and hand-foot syndrome [24]. A Phase II multicentre study of aflibercept in combination with cisplatin and pemetrexed for six cycles in patients with previously untreated advanced/metastatic non-squamous NSCLC, with maintenance administration of aflibercept, was to continue until disease progression, but was stopped prematurely because of a higher rate of reversible posterior leukoencephalopathy syndrome in the aflibercept group. Although ORR and

PFS were in accordance with the results of most historical first-line NSCLC studies, this combination of aflibercept–cisplatin–pemetrexed will not be further explored in NSCLC [25].

TKIs

Sorafenib (BAY 43-9006), the first small-molecule multi-target inhibitor approved for clinical use, is an orally active, unselective, multikinase agent that inhibits VEGFR, PDGFR, c-kit, Raf, and flt-3, not only directly restraining tumor growth but also blocking angiogenesis [26]. Sorafenib has shown activity in Phase III clinical trials in advanced renal cell carcinoma and hepatocellular carcinoma, and has therefore been approved by the FDA for treatment of advanced renal cell carcinoma and hepatocellular carcinoma [27–28]. Sorafenib combined with CT has also been investigated in NSCLC. Although a Phase II study suggested that single-agent sorafenib could benefit OS in patients with advanced untreated NSCLC [29], unfortunately, sorafenib in combination with cytotoxic agents for the treatment of patients with NSCLC failed to demonstrate a significant survival benefit in two Phase III studies. The first is the ESCAPE (Evaluation of Sorafenib, Carboplatin and Paclitaxel Efficacy in NSCLC; n = 926) study, evaluating sorafenib in combination with chemotherapeutic drugs in NSCLC, which was halted because no significant OS (10.7 months vs 10.6 months; P = 0.13) or PFS (4.6 months vs 5.4 months; P = 0.43) benefits were observed with sorafenib, and a higher mortality rate was observed when patients with squamous histology received sorafenib [30]. The second study, known as NExUS (NSCLC research Experience Utilizing Sorafenib; n = 5772), showed a PFS improvement, but not an OS improvement, for sorafenib plus gemcitabine/cisplatin vs CT alone in a first-line setting [31]. Based on the encouraging results of other Phase II trials [32], trials have also been conducted in a relapsed/refractory setting. Unfortunately, another Phase II trial also assessed sorafenib plus pemetrexed in a second-line setting with disappointing results [33]. Neither OS nor PFS improved in patients administered sorafenib plus pemetrexed vs pemetrexed alone, although post-hoc analysis suggested a marginal PFS benefit with the combination in patients who had previously received bevacizumab. The most promising approach seems to be the use of sorafenib as a single agent, particularly in previously treated NSCLC patients.

Other TKIs in combination with CT have also been tested for treatment of patients with NSCLC, but most outcomes are less than satisfactory.

VDAs

Vadimezan/ASA404 (Novartis) is a VDA. Unlike antiangiogenic agents, which inhibit the proliferation of new blood vessels, vadimezan induces hemorrhagic necrosis and a decrease in angiogenesis, aiming at cutting off the tumor's vasculature blood supply [34]. In a Phase I study of intravenous ASA404 administered in combination with paclitaxel and carboplatin in Japanese patients with NSCLC, tumor responses were noted, and the results support the further evaluation of ASA404 in Phase III studies in combination with paclitaxel and carboplatin in Japanese patients with advanced NSCLC [35]. However, a Phase III trial that tested vadimezanin in combination with CT in patients with advanced Stage IIIB/IV NSCLC, was stopped because interim analyses showed no increased OS benefit [36].

Targeting vascular endothelial cells

Endostar is a recombinant human endostatin with an additional nine-amino acid sequence at the N-terminal of the protein to help in protein purification, solubility, and stability [37]. This antiangiogenic drug is used in combination with standard CT for the treatment of advanced NSCLC in China, showing that endostar in combination with CT could successfully improve the response rate and lengthen the time to progression in patients with advanced [38–39]. Therefore, endostar was approved by the Chinese State Food and Drug Administration for use in combination with CT in patients with NSCLC [40]. In addition, endostar combined with platinum-based doublet CT for treating NSCLC improved ORR and DCR (P < 0.00001) by 14.7% and 13.5%, respectively, vs CT alone [41]. Recently, a Phase II trial of recombinant human endostatin in combination with concurrent chemoradiotherapy in patients with Stage III NSCLC demonstrated that the combination of endostar with chemoradiotherapy for patients with locally advanced NSCLC was feasible, and showed promising survival and local control rates [42]. Nevertheless, the exact mechanism through which endostar inhibits angiogenesis is not known. Additional randomized Phase II/III clinical trials are required to further study endostar in NSCLC treatment.

Discussion

From the above review, it is clear that intensive efforts have been made to study antiangiogenic agents over the last two decades, but the clinical yields remain poor. One of the key reasons for this may be the lack of predictive and prognostic biomarkers. However, since sequential administration avoids potential negative interactions between the two drugs used in combination and has been explored with EGFR-TKIs and CT [43], the combination schedules of other combinations should be investigated further. For example, a study evaluated the cytotoxicities of paclitaxel and sorafenib alone and in combination in NSCLC cell lines with KRAS or BRAF mutations, demonstrating that the synergistic antiproliferative activity

of paclitaxel followed by sorafenib was contrasted by the antagonistic activity of the reverse sequential combination. This study predicted that a combination treatment schedule of paclitaxel followed by sorafenib, which exhibited potent synergistic antitumor activities with acceptable tolerability in an *in vivo* model, can be used to treat NSCLC in patients with KRAS or BRAF mutations [44]. Coincidentally, another test, combining sorafenib with gemcitabine in EGFR-TKI-sensitive and EGFR-TKI-resistant human lung cancer cell lines, suggested that the sequence of gemcitabine followed by sorafenib exhibited the strongest synergism. It was explained that sorafenib arrested the cell cycle at the G1 phase, whereas gemcitabine caused arrest at the S phase. The molecular mechanism of this synergism is that the downstream signaling pathways that were initially activated by gemcitabine exposure were efficiently suppressed by the subsequent exposure to sorafenib. In contrast, the reverse of this sequential administration resulted in antagonism, which may be owing to differential effects on cell cycle arrest [45]. Hence, the synergistic and antagonistic effects may be explained by these effects between the two drugs, even for the weak points in clinical trials. The study also highlighted that the difference in the sequence-dependent anti-proliferative effects of sorafenib and gemcitabine may also result from growth signaling pathways. They found that gemcitabine enhanced the expression levels of molecules in downstream signaling pathways, for example, increasing the levels of p-AKT and p-ERK in tested cells, and these paths encourage tumor cell proliferation. Interestingly, the expression of p-ERK and p-AKT differed in response to each combination treatment. When gemcitabine was administered first, a significant decrease in p-AKT and p-ERK levels was observed in the tested cell lines. Conversely, when sorafenib was administered first, the levels of p-AKT and p-ERK decreased and then increased after subsequent exposure to gemcitabine. The sorafenib-induced decrease in p-ERK and p-AKT appears to be reversible. Another study also emphasized that the sequence of pemetrexed followed by sorafenib had a synergistic effect and an advantage over other sequences in EGFR TKI-resistant NSCLC cell lines [46]. These results may guide the development of sorafenib either as a single targeted therapy or in combination with cytotoxic CT drugs for the treatment of NSCLC. Similarly, another study, using nude mice with xenograft tumors, also showed that tumor growth in the concurrent administration group was lower than that of the endostar-first group when combined with docetaxel [47]. Although the combination of antiangiogenic agents with CT in NSCLC cell lines and tumor transplantation models is synergistic, there is still a complex path from the laboratory to clinical application, since only a few types of cell lines have been tested, and there may be different timetables based on different combinations, different histopathological types, and different gene mutations in patients with NSCLC. Thus, more time is needed to gain the experience to determine the correct personalized treatment.

Conclusion

Along with the development of insights into tumor angiogenesis, targeting the angiogenic pathway has been validated as an effective treatment approach for NSCLC. Bevacizumab is a relatively mature antiangiogenic agent for the treatment of NSCLC. Multi-targeted antiangiogenic agents, such as sorafenib, face many challenges in clinical trials in combination with CT. Biomarkers need to be discovered, and combination schedules need to be taken into consideration. For the personalized treatment of advanced NSCLC, optimal patient selection and identification of the appropriate biomarkers are crucial to developing the best treatment for the right patient. Furthermore, the right schedule for the combination of antiangiogenic agents and CT would provide opportunities for a more accurate and relevant clinical application in NSCLC treatment.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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DOI 10.1007/s10330-015-0072-1
Cite this article as: Chen SS, Lu S. Antiangiogenic agents combined with chemotherapy in non-small cell lung cancer. Oncol Transl Med, 2015, 1: 58–64.