Review

Targeting angiogenesis in non-small-cell lung cancer: a focus on current approaches and future developments



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Practice Points

- Despite recent advances in treatment, most patients with advanced disease have a median survival of approximately 10-12 months with aggressive chemotherapy. Standard platinum doublet cytotoxic chemotherapy has reached a therapeutic plateau.
- The advent of targeted agents as well as cytotoxic agents with a more favorable toxicity profile have shifted the paradigm of non-small-cell lung carcinoma (NSCLC) treatment, allowing new concepts such as maintenance therapy.
- Targeting the VEGF pathway, the major mediator of tumor angiogenesis, has become an attractive target in multiple malignancies, including lung cancer.
- The addition of bevacizumab to a platinum-based combination chemotherapy regimen is considered to be the first-line treatment in the management of metastatic nonsquamous NSCLC. The results of two pivotal randomized Phase III studies led to its approval by the US FDA: AVAIL and ECOG 4599.
- The PDGF superfamily consists of five members that act at two cell surface receptors with TK activity: PDGF-AA, -BB, -CC, -DD and -AB, which bind to PDGF- α and PDGF- β .
- PDGF pathway includes drugs such as sunitinib, an oral mTKI approved for the treatment of advanced renal cell carcinoma, imatinib-resistant or -intolerant gastrointestinal stromal tumors and advanced pancreatic neuroendocrine tumors. Sorafenib is another oral mTKI approved for treatment of unresectable hepatocellular carcinoma and advanced renal cell carcinoma.

Medicine part of

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- Another drug in this pathway includes cediranib. A third Phase III study designed to assess the addition of cediranib to carboplatin/gemcitabine concluded that multiple VEGF inhibition induced by the association of cediranib improved therapeutic efficacy at the expense of greater toxicity and treatment-related deaths. Studies are underway for motesanig and lifatinib.
- In the FGF pathway we already have Phase II studies with pazopanib and nintedanib that have shown tumor activity.
- There are new agents such as ramucirumab (IMC-121), a fully humanized monoclonal antibody that specifically binds to the extracellular domain of VEGFR-2 and has alredy been tested with carboplatin/paclitaxel for NSCLC with promising results.
- These are very promising drugs that have already gained approval for thyroid cancer and they are being tested on several tumors.
- Vatalanib has shown Phase II efficacy in NSCLC, on vandetanib unfortunately has negative Phase III trials for NSCLC. Other drugs in Phase II trials are cabozantinib foretinib BMS-690514.
- Aflibercept has already been approved for colon cancer, however when combined with docetaxel in NSCLC it did not show any benefit in survival.
- Antiangiogenesis therapy is blossoming with so many agents in development and multiple pathways to explore and research.
- The low toxicity profile of these agents in comparison with cytotoxic chemotherapy allows them to not only be given as monotherapy, but also in combination with conventional chemotherapy, as well as the opportunity to use these agents for new indications like maintenance therapy in NSCLC.
- The coming years are also essential in the search for predictive and prognostic factors for these agents to make them more effective and less toxic, and to optimize their use.

SUMMARY We know how important antiangiogenesis therapy can be in cancer treatment. However, it took some time before the first compound became approved. Currently, several agents are approved and used against cancer. Moreover, the possible number of clinical indications and agents that are in development is extraordinary. A lot of questions regarding angiogenesis in cancer still remain unanswered. One of the major weaknesses is the fact that most of the approved agents do not have a predictive or prognostic biomarker that can be used to tailor these novel agents in terms of inducing the best possible antitumor effect. Many of these new targeted agents inhibit several tumorigenesis pathways, but most of the time only one of these pathways is the main driver for cancer proliferation. In this article, we present the most current clinical information available in antiangiogenic therapy and the potential development in non-small-cell lung cancer.

Lung cancer remains the leading cause of cancer death worldwide. Approximately 85% of all lung cancers are non-small-cell carcinomas (NSCLC), and over 75% of patients present with locally advanced or metastatic disease [1]. Despite recent advances in treatment, most patients with advanced disease have a median survival of approximately 10-12 months with aggressive chemotherapy [2,3]. Standard platinum doublet cytotoxic chemotherapy has reached a therapeutic plateau. In addition, most patients with lung cancer have significant comorbidities and poor performance status, which affects their quality of life and capacity to tolerate intense cytoreductive treatments and/or prolonged therapy beyond four to six cycles of platinum doublet. However, the advent of targeted agents, as well as cytotoxic agents with a more favorable toxicity profile, have shifted the paradigm of NSCLC treatment and currently, maintenance therapy is a reality in thoracic oncology.

Angiogenesis plays a crucial role in NSCLC tumorigenesis. It is a delicate and tightly regulated process involving a series of mechanisms that lead to endothelial cell division and migration with the subsequent formation of new capillary vessels. Neoplastic processes such as NSCLC are characterized by a deregulation of this delicate balance caused, in part, by an excess activity of VEGF. VEGF induces the formation of aberrant vessels that supply the growing tumor mass with the necessary resources for disease progression and metastasis. VEGFs are crucial regulators of embryonic vasculogenesis as well as angiogenesis in adults. These molecules share a series of regulatory characteristics with other RTKs such as PDGF receptors (PDGFRs) and EGF receptors. Once activated, these receptors undergo dimerization with subsequent downstream activation of a TK domain which leads to transduction of intracellular signals that mediate cell growth and vasculature development. In addition to their role as intracellular growth signal transductors, VEGFs are also related to mechanisms of regulation of vascular permeability that lead to tissue edema, a property that has been attributed to the transtissue migration of carcinogenic cells during the metastatic process. VEGF-A is capable of inducing vascular permeability with a potency 50,000-times that of histamine [4]. There are five subtypes of VEGF receptors in mammals, three of which have been thoroughly

studied and associated with the pathophysiology of tumorigenesis: VEGF receptor (VEGFR)-1 is an upregulator of monocyte and macrophage migration. It is also credited with the donwregulation of VEGFR-2 expression. VEGFR-2 is implicated in physiologic as well as abnormal development, survival and migration of endothelial cells. VEGFR-3 is crucial for lymph vessel and endothelial cell formation, as well as acting as a function regulator. In addition, VEGFR-3 is associated with lymph node metastasis [5].

VEGF directly affects the properties of endothelial cells. It is critical for pulmonary and vascular function by mediating a vasodilator effect through nitric oxide and prostacycline synthesis. VEGF proangiogenic properties are attributed to an augmented expression of NOS [6]. The survival properties attributed to VEGF are fundamentally dependent on its activation of Bcl-2 [7], on other inhibitors of apoptosis and vascular morphogenesis [8], as well as on the activity of ILK and SRF [9]. Additionally, there are a number of cells that express VEGFRs, such as type II pneumocytes, which undergo growth, maturation and differentiation after being exposed to VEGFs [10,11].

The majority of NSCLC expresses VEGF [12], and the level of expression is directly related to disease progression [13] and decreased survival [14,15]. Stefanou et al. evaluated 88 patients with surgically resected NSCLC; VEGF expression was considerably high in 77% of the tumors [16]. From these and a number of other observations, it is known that NSCLCs are generally well vascularized tumors and the degree of vascularization is strongly associated with their metastatic potential [17]. Targeting the VEGF pathway, the major mediator of tumor angiogenesis, has become an attractive target in multiple malignancies, including lung cancer. Bevacizumab (Avastin[®], Genentech/Roche) a fully humanized recombinant monoclonal antibody that binds to VEGF in the circulation and thus decreases ligand binding, results in inhibition of VEGF signaling in cancer cells [2].

Currently, the addition of bevacizumab to a platinum-based combination chemotherapy regimen is considered the first-line treatment in the management of metastatic nonsquamous NSCLC. The results of two pivotal randomized Phase III studies cemented the integration of bevacizumab to standard chemotherapy protocols and led to its approval by the US FDA: AVAIL and ECOG 4599. ECOG 4599 evaluated the combination of bevacizumab plus carboplatin/paclitaxel on 878 patients with recurrent or advanced stage NSCLC. Patients in the experimental arm received bevacizumab at a dose of 15 mg/kg every 21 days plus carboplatin/paclitaxel versus a control arm of carboplatin/paclitaxel alone [18]. Patients in the bevacizumab-containing arm had a response rate (RR) of 35 versus 15% seen in the carboplatin/paclitaxel arm, a progression-free survival (PFS) of 6.2 versus 4.5 months as well as a longer overall survival (OS) 12.3 versus 10.3 months when compared to the carboplatin/paclitaxel arm.

AVAIL evaluated the combination of bevacizumab plus gemcitabine/cisplatin. A total of 1043 patients were enrolled: arm A received bevacizumab at a dose of 7.5 mg/kg, arm B at a dose of 15 mg/kg [19.20]. The study reported a 37.8% RR for arm A versus 21.6% in arm B. Although the incorporation of bevacizumab to the couplet gemcitabine/cisplatin was associated to a significant improvement in RR and PFS rates, no statistically significant improvement could be appreciated with regard to OS rates.

It is worth mentioning that even though both studies reported favorable results with the addition of bevacizumab, with regard to RR and PFS rates, a disjunction exists concerning the OS rates reported in them. The reason for such a discrepancy could be attributed to multiple factors, including that the patients in the AVAIL study had been previously exposed to strong courses of treatment that could have been responsible for attenuating the rate of response to the intervention [21]. Another factor to consider could be related to the proper and inherent effects of the carboplatin that was used in ECOG 4599 versus the cisplatin used in AVAIL [22]. Another cause could be linked to the use of taxanes. Preclinical evidence suggests that taxanes could act as vascular wall-disrupting agents [23]. The incorporation of bevacizumab to a paclitaxel regimen could have resulted in a synergistic effect of antiangiogenic control. Finally, many patients went on to receive additional treatments after disease progression which could have had an impact on the OS.

Since the development of bevacizumab, a plethora of other antiangiogenic agents have been investigated in an attempt to exploit this oncogenic pathway. The focus of this review is on new developments in antiangiogenesis for the treatment of NSCLC.

Antiangiogenic multikinase inhibitors

Since intracellular signaling pathways influence tumorigenesis, the use of agents with antiangiogenic properties that simultaneously inhibit multiple targets may have the additional advantage of maximizing antitumor activity while preventing the development of resistance to antineoplastic agents.

PDGF pathway

This pathway plays an important role for the integrity and function of the developing vasculature; it mediates through pericytes and vascular smooth muscle cells [24–26]. The PDGF superfamily consists of five members that act at two cell surface receptors with TK activity: PDGF-AA, -BB, -CC, -DD and -AB, which bind to PDGFR- α and - β . PDGF-AA recruits stromal cells and seems to induce VEGF secretion [27]. PDGF-BB is critical for vascular stabilization mediated by binding to surface PDGF- β TKRs expressed on vascular smooth muscle cells and recruiting of pericytes [28].

The relationship between VEGF and PDGF is becoming increasingly clear. From multiple observations, it has been inferred that VEGF secretion by pericytes and vascular smooth muscle cells occurs shortly after their recruitment. Additionally, it is suspected that PDGF secretion induces the recruitment of pericytes and mediates their integration to the tumor vascular architecture, which results in resistance to antiangiogenic therapy achieved by VEGF pathway blockers. Those tumors that lack coating by pericytes seem to be more sensitive to the anti-VEGF approach, suggesting that dual angiogenic pathway blockade could result in better response rates through an additive o synergistic effect. This has been demonstrated in experimental models [29].

Sunitinib

Sunitinib malate (Sutent[®]; Pfizer, NY, USA) is an oral, mTKI approved for the treatment of advanced renal cell carcinoma, imatinibresistant or -intolerant gastrointestinal stromal tumors and advanced pancreatic neuroendocrine tumors. Sunitinib selectively inhibits all three VEGF receptor subtypes (VEGFR-1, -2 and -3), PDGFR- α and - β , as well other important TKRs such as KIT, RET and FLT-3 [30]. Sunitinib was initially evaluated in a Phase II study in patients with stage IIIB/IV NSCLC that failed platinum-based chemotherapy [31]. A total of 63 patients were treated with sunitinib 50 mg daily 4 weeks-on and 2 weeks-off, reporting a RR of 11%, with 28% of the patients achieving stable disease (SD). Median PFS and OS were 12 and 23 weeks, respectively [31]. Fatigue (29%), myalgias (17%) and nausea (10%) were the most common grade 3-4 adverse effects (AE). Another Phase II study evaluated sunitinib as continuous daily dosing of 37.5 mg in 47 patients advanced NSCLC after disease progression with platinum-based chemotherapy. Only one patient had a response, and 23% had SD. Median PFS was 12 weeks and median OS was 37 weeks [32]. The treatment was better tolerated, with the most common grade 3-4 AE being fatigue (17%). From the total 110 patients included in both studies, three treatment-related deaths were reported.

As mentioned before, maintenance therapy has emerged as a treatment strategy in the management of advanced NSCLC. A Phase II study evaluated sunitinib as maintenance following treatment with standard doublet chemotherapy [33]. In a study where 84 patients were enrolled, 55 (65%) of them were able to receive sunitinib after first-line chemotherapy, reporting a median OS of 10.4 months. Of the 50 evaluable patients that received sunitinib maintenance, the RR was 8%; 40% attained SD, and 52% had progression of disease. The most frequently reported all-causality AE of any grade during sunitinib maintenance therapy were fatigue/asthenia (55%), diarrhea (36%), and nausea (32%) [33]. Sunitinib has also been evaluated in combination with pemetrexed in a Phase I study, reporting a median tolerated dose of 500 mg for pemetrexed and 37.5 mg of sunitinib daily; a RR of 24% was also reported. Therefore, sunitinib is considered to have promising activity in patients with advanced NSCLC; hence, it is currently being evaluated in two large Phase III studies. One of them as second-line agent with and without pemetrexed and another as single agent in maintenance therapy [34,35].

Sorafenib

Sorafenib (Nexavar[®]; Bayer, Leverkusen, Germany) is an oral mTKI approved for

treatment of unresectable hepatocellular carcinoma and advanced renal cell carcinoma. Besides the antiangiogenic activity against VEGFR-1 and -2, it also has activity against nonangiogenic kinases as B-Raf, RET, c-Kit and FLT-3 [36]. At one point, sorafenib was an attractive agent in NSCLC, since 15–30% of the tumors are reported to be *K-ras* mutant and the RAF serine—threonine kinases are the principal effectors of RAS [37,38]. Thus, there was hope that sorafenib could be a potential therapeutic agent in those K-ras mutant tumors. Unfortunately, studies revealed minimal clinical activity in this setting.

Sorafenib was evaluated as single-agent in a Phase II study as second- or third-line treatment in patients with relapsed or refractory advanced NSCLC. Of the 52 patients treated with sorafenib, 30 achieved a SD, but no responses were seen; median PFS was 2.7 months and the median OS was 6.7 months [39]. ESCAPE is a Phase III study that evaluated sorafenib plus carboplatin and paclitaxel as first-line therapy for unresectable stage IIIB or IV NSCLC. A total of 926 patients were enrolled, but the study was closed early because no improvement of RR nor survival were seen and there was an increased rate of bleeding events in patients with squamous histology [40].

To improve the patient selection, sorafenib was evaluated in a small cohort of 10 patients with K-Ras mutations after they failed at least one line of chemotherapy. Three PRs and three minimal responses were seen, with a median PFS of 3 months [41]. The most troublesome toxicities were hand-foot syndrome and diarrhea, although it was mostly grade 2. These results prompted the development of a Phase II study that enrolled 59 patients with advanced NSCLC with K-Ras mutation-positive tumors, after failure of at least one platinum-containing regimen [42]. At 6 weeks, seven PRs, 23 SD and 27 progression of disease were observed and, although the survival data seems to be disappointing, with a median PFS of 2.6 months and a median OS of 4.9 months, it is well known that patients with K-Ras mutations have a worse outcome when compared to wild-type K-Ras NSCLC patients [37,38,42].

Cediranib

Cediranib is an oral, mTKI with activity against VEGFR-1, VEGFR-2. VEGFR-3, PDGFR-A/B,

FBGFR-1 and c-kit [5]. Initial Phase I studies determined that the addition of cediranib at a dose of 45 mg daily to carboplatin/paclitaxel was safe and feasible [43]. Based on these data, a randomized Phase II/III study was performed to evaluate the use of carboplatin/paclitaxel in combination with cediranib versus placebo as a first-line treatment in patients with metastatic NSCLC [44]. Patients with squamous cell histology were included. A total of 45 patients were enrolled. Cediranib was administered at a dose of 45 mg daily but the dose had to be reduced to 30 mg after reporting unacceptably high toxicity rates. The results of the study were encouraging: RR of 38 versus 16% favoring cediranib over placebo and a PFS rate of 0.77 (95% CI: 0.56-1.08). However, the study was interrupted due to safety concerns, reporting an unacceptably high incidence of AEs such as hypertension, diarrhea, stomatitis, dyspnea, sensory neuropathy and even treatment-related deaths (4.5 vs 0.9%). Based on the information derived from this study and after considering the high RRs associated to the drug, there was general consensus to design a second study that evaluated the use of cediranib at a lower dose of 20 mg to reduce toxicity-related effects while inducing remission [21]. The protocol design used for this study was similar to its predecessor. Nevertheless, the study was terminated after an interim analysis revealed subtherapeutic dosage and failure to meet its primary end points. A third Phase III study was designed to assess the addition of cediranib to carboplatin/ gemcitabine versus carboplatin/gemcitabine alone as first-line treatment for patients with advanced stage NSCLC, including patients with squamous cell histology [45]. A total of 87 patients were evaluated. There were no differences in RR between the two study arms. Slightly better results were observed with regard to PFS and OS favoring cediranib: a PFS of 6.3 versus 4.5 months. OS rate of 11.8 months for cediranib versus 9.9 months for the placebo arm. According to the data attained from these studies, it has been concluded that multiple VEGF inhibition induced by the association of cediranib with a platinum-based chemotherapy protocol results in an improved therapeutic efficacy at the expense of greater toxicity and treatment-related deaths. The reduction in the dose of cediranib to placate these concerns resulted in subpar efficacy rates.

Motesanib

Motesanib (AMG 706; Amgen, CA, USA) is a mTKI that shows activity against VEGFR-1, -2, -3, PDGFR-B, c-kit and RET [46]. Two studies are currently underway that try to assess the use of motesanib in chemotherapy-naive patients with advanced stage NSCLC. One of them is a three-arm randomized Phase II study that evaluates the efficacy of motesanib versus bevacizumab given in combination with carboplatin/paclitaxel in 181 patients assigned to one of three treatment arms [47]. Neither of the motesanib arms were demonstrated to have superior response rates or survival advantage over the bevacizumab plus chemotherapy arm. Common side effects related to the medication were diarrhea, dehydration, fatigue, anorexia and nausea; all more frequently seen among patients assigned to the continuous administration of motesanib. It is also worth mentioning that the study had a number of limitations, fundamentally related to the small number of patients that was assigned to treatment and control arms and the fact that it was not statistically powered to detect a difference in RR among the groups.

MONET1, a Phase III study, evaluated the addition of motesanib to carboplatin/paclitaxel versus carboplatin/paclitaxel plus placebo [48]. A total of 1090 treatment-naive patients enrolled, reporting a higher partial response rates for the motesanib arm when compared to the placebo arm (40 vs 26%), but similar OS between arms (13 vs 11 months; p = 0.14). The incidence grade 3/4 AE was 73% for motesanib versus 59% for the control group, reporting an increased incidence for neutropenia (22% associated to motesanib vs 15% associated to the placebo arm), diarrhea (9 vs 1%), hypertension (7 vs 1%) and colecystitis (3 vs 0%).

Linifanib

Linifanib (ABT-869; Abbott, IL, USA) is a mTKI that targets VEGFR-1, -2, -3 and PDGFR [49]. A randomized Phase II study evaluated the safety and activity of linifanib in a cohort of 139 patients with NSCLC with prior lines of systemic therapy [50]. Patients were assigned to two treatment arms that differ in the dose of linifanib to which they were to be exposed: arm A received 0.10 mg/kg daily (low dose) versus arm B, which received 0.25 mg/kg daily (high dose). Median time to progression was reported at 3.6 months (3.6 vs 3.7 months),

median PFS of 3.6 months (3.5 vs 3.6 months) and median OS of 9 months (10 vs 8.3 months). The most commonly reported grade 3/4 AE was hypertension at 14%. Other common AEs were fatigue (42%), anorexia (38%), hypertension (37%), diarrhea (32%), nausea (27%), palmar–plantar erythrodysesthesia (24%) and proteinuria (22%) [50].

Experimental triple-targeted inhibition of angiogenesis

In addition to VEGF, PDGFR and FGF receptor (FGFR) are also involved in angiogenesis and play a crucial role in resistance to anti-VEGF therapy. The capacity to simultaneously interfere with these three signaling pathways should theoretically impair an effective angiogenesis.

FGF pathway

FGFs have a crucial role in tumor angiogenesis. The pathway accounts for the proliferation, migration and cell differentiation during embryonic stages of development. In adults, FGFs are crucial to mediate tissue repair processes and response to injury [51]. FGF's angiogenic property is mediated through activation of endothelial cells, pericytes, vascular smooth muscle cells and recruitment of monocytes. In addition, it has been observed that FGF and PDGF-BB promote angiogenesis by acting synergistically, which could play a role in the resistance to VEGF inhibition. This relationship was previously reported in a number of studies. Batchelor et al. evaluated the efficacy of the pan-VEGFR, PDGFR and FGFR TKI inhibitor cediranib on patients with relapsed glioblastoma multiforme. The study was able to demonstrate that disease progression was associated to an increase in serum FGF-B levels among other markers [52]. According to Yoshiji et al. FGF-B can compensate for the VEGF blockade and induce angiogenesis in transplanted tumors [53].

Pazopanib

Pazopanib is an oral TK small molecule which targets VEGFR-1, -2, -3, PDGFR- α , - β and FGFR-1 [54]. Currently there are multiple ongoing clinical studies evaluating pazopanib in advanced NSCLC and in the adjuvant setting. A Phase II study evaluated pazopanib as single agent in the neoadjuvant setting in 35 patients with Stage I/II NSCLC. There was evidence of tumor reduction in 86% of the patients. But only three of 35 patients achieved a PR [55].

Nintedanib

Nintedanib (Vargatef[®]; Boehringer Ingelheim, Germany), formerly known as BIBF1120, is an oral small molecule TKI of VEGFR-1-3, PDGFR- α/β , FGFR-1–3, Src, and FLT-3 [56]. A Phase II study evaluated 73 patients with chemotherapy refractory advanced NSCLC. Median PFS was 6.9 weeks and OS was 21.9 weeks [57]. A Phase I study evaluated the combination of nintedanib plus pemetrexed in second-line treatment for platinum-resistant NSCLC. The study concluded that both agents can be administered at maximal dosages, with nintedanib given at 200 mg orally twice daily continuously [58]. There are currently two ongoing Phase III studies evaluating the efficacy of nintedanib: the LUME-Lung 1 trial and LUME-Lung 2 trial. LUME-Lung 1 (NCT00805194) is a multicenter, randomized, double-blind, Phase III study assessing the efficacy of nintedanib as secondline treatment when given in combination with a standard docetaxel regimen versus placebo in combination with docetaxel in patients with stage IIIB/IV or recurrent NSCLC. It has an estimated enrollment of 1300 patients and its primary completion date was January 2013. LUME-Lung 2 (NCT00806819) is a randomized, double-blind, Phase III study evaluating the efficacy of nintedanib plus pemetrexed versus pemetrexed alone as secondline treatment in patients with stage IIIB, IV or recurrent NSCLC with nonsquamous histology. It had an estimated enrollment of 717 patients with a primary completion date in May 2013.

VEGFR-2-specific inhibition Ramucirumab

Ramucirumab (IMC-121B; Eli Lilly, IN, USA) is a fully humanized monoclonal antibody that specifically binds to the extracellular domain of VEGFR-2 [59]. In preclinical models, the agent has effectively proven to block the migration and proliferation of endothelial cells. There are a number of ongoing studies evaluating the efficacy of ramucirumab. A Phase II study currently underway is evaluating the efficacy of the drug in combination with carboplatin/ paclitaxel as a first-line approach on treatmentnaive patients with advanced stage NSCLC (NCT00735696). An ongoing four-arm



Phase II study is assessing the efficacy of pemetrexed or gemcitabine plus carboplatin/ paclitaxel with or without ramucirumab as first line treatment for recurrent or advanced stage NSCLC (NCT01160744). REVEL, is an ongoing Phase III study evaluating the efficacy of ramucirumab on patients with NSCLC that have progressed on a platinumbased chemotherapy regimen (NCT01168973). Interim data analysis from two Phase II studies has revealed the following results. The first of such studies, evaluated the efficacy of ramucirumab in combination with first-line pemetrexed/platinum-based chemotherapy on 140 chemotherapy-naive patients with advanced NSCLC. Patients were randomized based on histology (nonsquamous NSCLC: treatment arms A and B; squamous NSCLC: treatment arms C and D). Arm A was allocated to receive pemetrexed in combination with carboplatin or cisplatin once every 3 weeks. Arm B was allocated to receive carboplatin/pemetrexed doublet or cisplatin plus ramucirumab once every 3 weeks. PFS was reported at 4.3 months in arm A versus 6.3 months in arm B (HR: 0.48; 90% CI: 0.31-0.74). Disease control rate (DCR = CR + PR + SD) was reported at 72% for arm A versus 87% for arm B [60]. The second study evaluated the efficacy of ramucirumab plus carboplatin/paclitaxel as first-line treatment for advanced stage NSCLC. A total of 40 patients were allotted to receive ramucirumab (10 mg/kg), carboplatin (AUC = 6), and paclitaxel (200 mg/m^2) on day 1 of a 3-week cycle for up to six cycles, followed by maintenance therapy with ramucirumab. PFS was reported at 7.9 months with an overall disease control rate of 90% [60].

Other multitargeted TKIs
 Vatalanib

Vatalanib is an oral small molecule TKI that prevents activation of VEGFR-1, -2, -3, PDGFR and c-kit [61]. A Phase II study evaluated the efficacy of vatalanib in patients with stage IIIB/IV NSCLC refractory or relapsed after one prior first-line platinum chemotherapy or chemoradiotherapy. The study enrolled a total of 112 patients. A total of 54 patients were randomized to receive vatalanib 1250 mg orally daily and 58 patients received 500 mg in the morning and 750 mg in the afternoon. Both arms were treated continuously until disease progression or unacceptable toxicities. AEs leading to discontinuation of therapy occurred in 11 (20%) patients in the once-daily arm compared to 16 (29%) in the twice-daily arm. Median treatment duration was 64 days in the once-daily arm and 84 days in the twice-daily arm. In the once-daily arm one (2%) patient achieved PR, and 27 (50%) attained SD for 4–12 weeks. In the twice-daily arm, three (5%) patients achieved PR, and 37 (66%) had SD for 4–12 weeks. Median PFS was 2.1 months for the once-daily arm and 2.8 months for the twicedaily arm [62].

Vandetanib

Vandetanib (Caprelsa[®]; AztraZeneca, London, UK), is a small molecule TKI that targets EGFR, VEGFR and RET. Phase I studies in patients with solid tumors demonstrated that vandetanib can be given at a dose of 300 mg orally daily [63,64]. A Phase II study enrolled 168 patients with locally advanced or metastatic (stage III/IV) NSCLC patients after failure of at least one line of platinum-based chemotherapy. Patients were randomized to receive vandetanib 300 mg daily or gefitinib 250 mg daily until disease progression or unacceptable toxicity. The study allowed patients to switch treatment arm after a washout period of 4 weeks. Median PFS was 11 versus 8.1 weeks for vandetanib and gefitinib, respectively (HR 0.69). Objective responses were seen in 8% of patients treated with vandetanib compared to 1% treated with gefitinib. The safety profiles of both vandetanib and gefitinib were similar [65]. Two subsequent Phase II studies evaluated the combination of vandetanib with chemotherapy in patients with advanced of metastatic NSCLC. The first study enrolled 127 patients with stage IIIB/IV NSCLC after failure with first-line platinum-based chemotherapy. Patients in this double-blind study were randomized to receive vandetanib 100 mg orally daily plus docetaxel 75 mg/m^2 intravenously every 3 weeks (n = 42, arm A), vandetanib 300 mg orally daily plus docetaxel 75 mg/m² intravenously every 3 weeks (n = 44, arm B), or docetaxel 75 mg/ m^2 intravenously every 3 weeks alone (n = 41, arm C). Median PFS was 18.7 weeks for vandetanib 100 mg plus docetaxel (HR: 0.64), 17 weeks for vandetanib 300 mg plus docetaxel (HR: 0.83), and 12 weeks for docetaxel alone [66,67]. The second Phase II study evaluated the

combination of vandetanib plus carboplatin/ paclitaxel as first-line treatment in patients with stage IIIB/IV NSCLC. The study enrolled 181 patients and they were randomly assigned 2:1:1 to receive vandetanib 300 mg orally daily (n = 73, arm A), vandetanib 300 mg orally daily plus carboplatin/paclitaxel intravenously every 3 weeks (n = 56, arm B) or carboplatin/ paclitaxel every 3 weeks (n = 52, arm C). Arm A of vandetanib monotherapy had to be discontinued prematurely due to preplanned interim analysis of PFS by a data safety monitoring committee due to a HR of 1.33. Median PFS was 24 weeks for the vandetanib plus carboplatin/paclitaxel, and 23 weeks for the carboplatin/paclitaxel alone (HR 0.76). OS was not significantly different between arm B and C [67].

A large double-blind randomized Phase III study ZODIAC enrolled 1391 patients with stage IIIB/IV NSCLC who had progressed after first line treatment. Patients were randomly assigned to vandetanib 100 mg orally daily plus docetaxel 75 mg/m² intravenously every 3 weeks (n = 694) or docetaxel 75 mg/m² alone (n = 697). Patients were treated for a maximum of six cycles. Median PFS was significantly improved in patients treated with vandetanib plus docetaxel compared to docetaxel alone (4 vs 3.2 months; HR: 0.79). The addition of vandetanib to docetaxel also resulted in a significant improvement in RR (17 vs 10%, p = 0.0001). There was no significant difference between treatment groups for OS (HR 0.91) [68].

Another large double-blind randomized Phase III study ZEST evaluated whether vandetanib prolonged PFS compared to erlotinib in patients with previously treated stage IIIB/IV NSCLC. A total of 1,240 patients were randomly assigned to vandetanib 300 mg orally daily or erlotinib 150 mg orally daily until disease progression or unacceptable toxicity. There was no significant improvement in PFS for patients in either arm, 2.6 months for vandetanib and 2 months for erlotinib (HR: 0.98). Median OS was 6.9 months for vandetanib and 7.8 months for erlotinib (HR: 1.01) [69].

Cabozantinib

Cabozantinib (XL184; Cometriq[®], Exelixis, CA, USA) is a small molecule inhibitor of VEGFR-2, MET, RET, c-KIT and FLT-3 that has shown preclinical evidence of antitumor activity in experimental models of lung cancer [70]. A Phase II study has shown clinical activity of cabozantinib with a disease control rate of 42% at 12 weeks treatment [71]. This compound has also shown clinical activity in other tumor types. In fact, it has recently being approved for the treatment of medullary thyroid carcinoma.

Foretinib

Foretinib (GSK1363089; GlaxoSmithKline, London, UK) is a small molecule kinase inhibitor that shows activity against hepatocyte growth factor and VEGF receptor TK families, with additional activity against KIT, FLT-3, PDGFR- β and Tie-2 [72]. An ongoing randomized Phase I/II study is evaluating the safety of erlotinib with or without foretinib and also to determine its efficacy as treatment on a nonchemotherapy-naive population with locally advanced or metastatic NSCLC (NCT01068587).

BMS-690514

BMS-690514 is a selective pan-HER and VEGFR-2 inhibitor in early development that has shown activity against NSCLC according to data obtained from a Phase I multicenter study [73]. Further evaluation of the effectiveness of BMS-690514 in NSCLC xenografts revealed significant inhibition of tumoral growth as stand-alone treatment and exhibited marked tumor growth-delay when administered in an adjuvant setting concomitantly with radiation, which could be related to a synergistic effect [74].

MGCD265

MGCD265 is a novel multikinase inhibitor that targets MET and VEGFR tyrosine kinases (VEGFR-1, -2 and -3) as well as Tie-2 and Ron and is currently undergoing Phase I and Phase I/II combination clinical studies (combined with erlotinib and docetaxel) [75]. Data obtained from preclinical studies suggest that the administration of MGCD265 results in better antitumor activity than the standalone treatment of erlotinib or docetaxel. Moreover, the conjunct administration is well tolerated. Further evaluation of this drug is needed.

VEGF trap

Aflibercept

Aflibercept (Zaltrap[®]; Regeneron, NY, USA), is a fully humanized recombinant fusion protein composed of the extracellular domains of VEGFR-1 and -2 fused to the constant region of IgG1 with affinity for VEGF-A, -B and PGF [76]. This molecule binds with higher affinity to VEGF-A than bevacizumab [77]. Aflibercept has been recently approved for the secondline treatment of metastatic colorectal cancer in combination with 5-FU and irinotecan. A Phase II study in heavily pretreated patients with lung adenocarcinoma reported minor single-agent activity and good tolerance [78]. The ziv-aflibercept versus placebo in patients with second-line docetaxel for locally advanced or metastatic NSCLC (VITAL) was a large randomized Phase III study aimed to compare the addition of aflibercept to docetaxel or docetaxel alone in platinum-pretreated patients with advanced or metastatic NSCLC. A total of 913 patients were randomly assigned to either docetaxel/aflibercept doublet (n = 456) or docetaxel alone (n = 457). Prior bevacizumab had been administered in 12% of patients. Median PFS was statistically superior in the aflibercept containing group 5.2 versus 4.1 months (HR: 0.82). There were no differences in OS between the two arms (10.1 vs 10.4 months, HR 1.01). Aflibercept plus docetaxel had a worse toxicity profile with grade 3/4 AEs in 71.5 versus 49.7% in the docetaxel alone group. Fatal events also occurred more often in the aflibercept group 7.1 versus 4% [79].

Discussion

We need a better understanding of tumor pathophysiology in NSCLC and the elucidation of mechanisms behind angiogenesis represent another potential therapeutic approach of this dismal disease and, as such, constitutes the point of interest of a number of ongoing trials. To date, bevacizumab is the only antiangiogenic agent that has demonstrated a significant improvement in OS rates in patients with NSCLC. Although considered to be a victory in the management of this entity, the discovery of more efficient blockers of alternate pathways of angiogenesis remains of crucial importance mainly for two reasons. First, because of the eventual and unavoidable resistance to VEGF pathway blockade with bevacizumab; and second, because of the necessity to find agents that comparatively do better to improve PFS and OS rates in NSCLC.

Even though dual or triple blockade

of angiogenic pathways should relate to remarkably improved RR from a theoretical perspective because more pathways have been blocked to better destroy tumor growth, the multitarget approach of VEGF and PDGF or FGF has not resulted in better OS rates from what has been inferred from experimental models. The same cannot be said with regard to RR and PFS outcomes, which have shown noticeable benefit from dual inhibition. There are a number of hypotheses that could explain this lack of improvement regarding OS. First, VEGFR blockade could result in compensatory upregulation of serum VEGF, which would result in exaggerated tumor growth when interrupting the antiangiogenic agent during disease progression, meaning the survival gets impaired. Second, response to the agent, and thus OS could be directly related to the magnitude of the cell population that is resistant to angiogenic inhibition. Those tumors that respond better to the treatment would do so in function of the population of cells sensitive to vascular blockade. Perhaps the third most important reason is the lack of a predictive or prognostic biomarker for bevacizumab and all other novel compounds for which moiety has antiangiogenic properties. In other words, we have not been able to establish an antiangiogenic personalized approach something that we are doing very well not with other antineoplastic agents like TKI or ALK inhibitors. This is the reason why not all patients respond well to bevacizumab, or there have been contradictory results when this agent has been used (e.g., in lung cancer: ECOG 4599 vs AVAiL results for OS; in breast cancer: ECOG2100 vs AVADO vs RIBBON-1 studies in terms of the magnitude of PFS) or there have not been a consistent moderate/great activity from other new antiangiogenic molecules across the board. Hence, the importance of continuing the research efforts to tailor or individualize the therapeutic approach.

Another consideration is to limit the number of multicenter Phase III large clinical trials until we can identify the proper biomarkers, this is maybe a better strategy instead to do like now to launch a large trial and try to see if we discover the biomarker after we get good results that most of the time does not happen or again in the case of bevacizumab even if happen we are not sure which one is the biomarker. Perhaps

Table 1. Results of pivotal Phase II and Phase III clinical trials evaluating antiangiogenic receptor tyrosine kinases in advanced non-small-cell lung carcinoma.

Agent	Phase	n	Line of treatment	RR (%)	SD (%)	PFS	OS	Ref.
Sorafenib	II	52	>2 chemotherapy regimens	NR	57.7	2.7 months	6.7 months	[xx]
Sorafenib plus carboplatin/paclitaxel (arm A) vs placebo plus carboplatin/ paclitaxel (arm B)	III	926 A: 464 B: 462	Chemotherapy- naive	A: 27 B: 23	A: 46 B: 48	A: 4.6 months B: 5.4 months	A: 10.7 months B: 10.6 months	[xx]
Sorafenib	II	59	K-RAS positive, >1 chemotherapy regimen	7	23	2.6 months	4.9 months	[xx]
Sunitinib	II	63	>1 chemotherapy regimen	11	28	12 weeks	23 weeks	[xx]
Sunitinib	II	47	>1 chemotherapy regimen	0.21	23	12 weeks	37 weeks	[xx]
Sunitinib as maintenance	II	50	Maintenance after Carboplatin/ Paclitaxel	8	40	NR	10.4 months	[xx]
Cediranib 30 mg plus carboplatin/ paclitaxel (arm A) vs placebo plus carboplatin/paclitaxel (arm B)	II	45	Chemotherapy- naive	A: 38 B: 16	NR	HR: 0.77	NR	[xx]
Cediranib plus gemcitabine/carboplatin (arm A) vs gemcitabine/carboplatin alone (arm B)	II	87 A: 58 B: 29	Chemotherapy- naive	A: 20 B: 18	NR	A: 6.3 months B: 4.5 months	A: 11.8 months B: 9.9 months	[xx]
Motesanib (arm A: continuously; arm B: 5 days on/2 days off) plus carboplatin/ paclitaxel vs bevacizumab plus carboplatin/paclitaxel	II	181 A: 59 B: 62 C: 60	Chemotherapy- naive	A: 30 B: 23 C: 37	A: 35 B: 50 C: 42	A: 7.7 months B: 5.8 months C: 8.3 months	A: 14 months B: 12.8 months C: 14 months	[xx]
Motesanib plus carboplatin/paclitaxel (arm A) vs placebo plus carboplatin/ paclitaxel (arm B)	III	1090	Treatment-naive	A: 40 B: 26	NR	A: 5.6 months B: 5.4 months	A: 13 months B: 11 months	[xx]
Linifanib (arm A: 0.10 mg/kg/d; arm B: 0.25 mg/kg/d)	II	139 A: 65 B: 74	1–2 previous chemotherapy regimens	A: 3.1 B: 6.8	NR	A: 3.5 months B: 3.6 months	A: 10 months B: 8.3 months	[xx]
Pazopanib	II	35	Treatment-naive within 6 months.	8.7 PR	88.6	NR	NR	[xx]
Nintedanib	II	73		NR	48	6.9 months	21.9 months	[xx]
Ramucirumab plus pemetrexed/ platinum (arm A) vs pemetrexed/ platinum (arm B)	II	140	Chemotherapy- naive, nonsquamous NSCLC	DCR: A: DCR: B: 8	72 37	A: 4.3 months B: 6.3 months	NR	[xx]
Ramucirumab plus carboplatin/ paclitaxel	II	40	Treatment-naive	DCR: 90	%	7.85 months	NR	[xx]
Cabozantinib	II	59	<3 lines of systemic therapy	9	49	NR	NR	[xx]
Vatalanib	II	112	Second line	2 q.d. 5 b.i.d.	50 q.d. 66 b.i.d.	2.1 months q.d. 2.8 months b.i.d.	NR	[xx]
Vandetanib plus docetaxel vs docetaxel alone	III	1391	Second line	17 vs 10	NR	4 months vs 3.2 months	NR	[xx]
Vandetanib vs erlotinib	III	1240	Second line	NR	NR	2.6 months vs 2 months	6.9 months vs 7.8 months	[xx]
Aflibercept plus docetaxel vs docetaxel	111	913	Second line	23.3 vs	38.6 vs	5.4 months vs	10.1 months vs	[xx]

we should give more strength to more Phase II studies, where we can enroll the patients with the antiangiogenic agent based on postulated antiangiogenic markers to give a more logical and rational therapy.

The triple inhibition of vascular-formation pathways achieved through agents against TKRs, such as nintedanib, could result in better outcomes in the near future by offering a more thorough blockade of tumor angiogenesis. There are numerous studies underway trying to find new agents that simultaneously block multiple alternate pathways of angiogenesis, which offers an attractive outlook for the future of this field. One caveat to the former alternative that must be considered is toxicity. Although the dual blockade can induce higher response rates, this is negatively balanced with a worse toxicity profile in several trials. This is another reason to find strong predictive biomarkers that can outweigh the benefit of treatment over the risks for toxicity.

Conclusion

In summary, we can say that antiangiogenesis therapy is blossoming with so many agents in development, at the same time we are looking for 'real' targets so that we can predict significant responses that may translate into prolonged survival. In that regard, we may have to change our strategies when we design clinical trials. The low toxicity profile of these agents in comparison with cytotoxic chemotherapy allows them to not only be given as monotherapy, but also in combination with conventional chemotherapy,

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as well as the opportunity to use these agents for new indications, such as maintenance therapy in NSCLC. The coming years will also be essential in the search for predictive and prognostic factors for these agents to make them more effective and less toxic and to optimize their use.

Future perspective

We believe that this field is going to evolve tremendously in the next 5-10 years. These antiangiogenic agents not only seem to have efficacy but also to be nontoxic and have already been proven, in the case of lung cancer, that they can be use as maintenance therapy increasing survival and contributing to make a lung cancer a chronic disease. The challenges will be in the fact that there is only a selected population of patients that will benefit from these agents more than the median survival average that is the one for the selected and unselected population. These drugs can have a great role if we are able to customize to use.

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