PERSPECTIVE

Anti-angiogenic treatments in advanced NSCLC: back to the drawing board

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Sorafenib is a multi-kinase inhibitor, targeting the serine-theronine kinases c- and b-raf, and the tyrosine kinases VEGFR1-3, PDGF-beta, c-kit, RET and fms-like tyrosine kinase receptor 3 (Flt3). Thus, it inhibits multiple signaling pathways that are involved in tumor growth and spread, including tumor cell proliferation and survival, and angiogenesis. Sorafenib has proven efficacy as a single drug treatment for hepatocellular carcinoma (1) and renal cell carcinoma (2). It is being tested as a treatment for several other tumors, either as a single agent or as an addition to other therapeutic reagents. Several studies have reported its use in NSCLC patients.

The recently reported NExUS study compared gemcitabine-cisplatin doublet for advanced NSCLC, given with sorafenib or placebo (3). No survival advantage was seen. PFS by investigator assessment was longer with sorafenib (6 *vs.* 5.5 months) but an independent radiologic review conducted on 46% of the study participants did not confirm this finding. Two years ago, the ESCAPE study, reported by Scagliotti *et al.* reported no advantage to the addition of sorafenib to carboplatin and paclitaxel, neither OS nor PFS (4). The ESCAPE study was halted after an interim analysis that indicated the study would probably not demonstrate an advantage to the sorafenib arm. Furthermore, a preplanned analysis of the different histologic subgroups of NSCLC found higher mortality in the sorafenib treated squamous cell population (SCC; OS of 8.9 months; 95% CI, 6.3 to 13.9 months) compared to their control arm (13.6 months; 95% CI, 9.6 months to not estimable; HR 1.85; 95% CI, 1.22 to 2.81). PFS was also shorter for the sorafenib treated SCC patients. Regarding other histologies, OS and PFS was comparable between the sorafenib treated and the control

group. Following the report from the ESCAPE study, NExUS investigators modified their study to exclude SCC patients. Indeed, OS in the ESCAPE trial was slightly higher in the sorafenib treated non-squamous patients (11.5 months, 95% CI, 9.7 to 14.8 months) compared to their control (10.2 months, 95% CI, 9.1 to 11.5 months), making it plausible that sorafenib might benefit these patients.

The detrimental effect of an anti-angiogenic drug in SCC lung cancers was seen previously with bevacizumab, with four severe pulmonary hemorrhagic events in a group of 13 SCC patients in an early trial (5) causing squamous cell patients to be excluded from further bevacizumab studies. A recent single arm study evaluating delayed administration of bevacizumab only to squamous cell lung cancer patients reported one significant pulmonary hemorrhage in 31 participants (6), thus not abolishing the concern of this risk in SCC. However, the worse outcome of SCC in the ESCAPE trial is not a result of a high incidence of pulmonary hemorrhage (4). Since the mechanism by which sorafenib increases mortality in SCC is not known, it is conceivable that the same mechanism is at work to some extent also in non-squamous lung cancers, causing the disappointing results of the ESCAPE and now the NExUS. In this context, it is important to note preclinical studies demonstrating enhanced aggressiveness of cancer cells surviving anti-angiogenic treatment (7,8), possibly through upregulation of alternate molecular pathways that increase cell invasion and survival capacities.

Sorafenib thus joins a growing list of angiogenesis inhibitors that failed to improve the efficacy of standard treatment regimens when administered to unselected NSCLC patients or to non-squamous NSCLC patients (9-14). These small tyrosine kinase inhibitors (TKIs) were regarded as the next generation of anti-angiogenic drugs following bevacizumab. Being small molecules allows them to penetrate into poorly perfused tissues such as cancer. Thanks to their shorter half-life, toxicities can be easily controlled. Designed to inhibit a common kinase domain, most of these TKIs inhibit a common set of targets including the VEGF receptors 1-3, PDGFR and c-Kit. Since all these molecules are involved in the process of angiogenesis, this promiscuity was

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also regarded as increasing the chances of a higher efficacy. The common failure of the anti-angiogenic TKIs should force us to look closer, trying to see what is the mechanism of failure.

The synergism between an angiogenesis inhibitory molecule and chemotherapy is actually counter-intuitive. If angiogenesis is inhibited, chemotherapy delivery to the tumor would be reduced and so would the treatment efficacy. Several potential explanations have been proposed for the synergism observed between bevacizumab and carboplatin and paclitaxel (15). Rapid vessel normalization and reduced blood vessel permeability by VEGFR inhibition, resulting in reduced intra-tumor pressure could improve chemotherapy delivery to tumors and not reduce it (16). Thus, before anti-angiogenic treatment causes elimination of the vessels that perfuse a tumor, a window of opportunity might exist when tumor perfusion and drug delivery is increased. This putative mechanism has gained a lot of attention, but direct evidence for its role in human cancer is lacking. In contrast, axitinib decreased tumor exposure to concomitantly given cyclophosphamide (17), and sunitinib treatment only enhanced diffusion parameters and not tumor perfusion (18). It can thus be speculated that an anti-angiogenic-drug holiday prior to chemotherapy administration might enhance chemotherapy delivery and treatment efficacy. The requirement for an anti-angiogenic-drug holiday was tested in a recently completed phase I-II trial combining axitinib with cisplatin/pemetrexed (NCT00768755). Specific sequence and interval might be required for synergism stemming from sequential blockage of signaling pathways, according to a study performed in a cell culture model (19).

Anti-angiogenic drugs and chemotherapy synergism might be secondary to enhanced killing of tumor endothelial cells (17,20,21), suggesting they should be given concurrently. Taxanes have been noted as drugs with endothelial cytotoxicity (21). A different mechanism suggested indicates circulating endothelial progenitor cells as the target of combined chemotherapy and VEGF pathway inhibitors (22). Such a mechanism would be relevant only for drugs that induce a surge of circulating endothelial progenitor cells, a phenomenon seen mainly with taxanes. In this regard, the failed ESCAPE trial had a better chance of demonstrating the efficacy of sorafenib in addition to chemotherapy. The available evidence indicates that combining anti-angiogenic drugs given continuously with chemotherapy is unlikely to be synergistic.

The major advances in the treatment of advanced NSCLC in recent years were in the arena of personalized medicine, allowing the choice of targeted agents to specific patients according to the presence or absence of sensitizing genetic abnormalities in the cancer genome. Anti-angiogenic treatment, although promising, cannot be targeted to patients most likely to benefit from it as no predictive markers have been validated. In an analysis of the E4599 trial, VEGF plasma levels were predictive for response to bevacizumab but not predictive of a survival benefit (23). In contrast, VEGF plasma levels were negatively correlated with PFS in patients treated with vandetanib (24), and a greater increase in VEGF plasma levels with vandetanib treatment predicted worse outcome (25). Placental growth factor elevation showed a trend to be predictive of response to motesanib (26). Polymorphisms in the *VEGF* gene, as well as in the *ICAM-1* and *WNK1* genes were found to correlate with bevacizumab-related improved survival (27), and *VEGF* and *VEGFR* polymorphisms correlated with sunitinib-treated patients clinical outcome (28). An increase in ICAM-1 levels with treatment was associated with a better PFS in vandetanib treated NSCLC patients (25). Analysis of E4599 samples revealed improved PFS with bevacizumab for patients with low baseline levels of ICAM-1, and improved OS with bevacizumab for patients with stable levels of E-selectin (23). Baseline levels of hepatocyte growth factor and of IL-12 were predictive of response to pazopanib (29). Tumor mRNA levels of LDH-A, Glut-1 and VEGFR-1 were found to predictive of response to the VEGFR inhibitor PTK787/ZK 222584 in colorectal cancer patients (30). Early changes in tumor hypoxia assessed by 18F-Misonidazole-PET (31), as well as changes in pVEGFR2 immunostaining (32) were reported to be a biomarker of pathological response to bevacizumab-based neoadjuvant therapy for breast cancer. Novel techniques such as PET imaging of VEGF itself could provide useful predictive tools (33). Interestingly, sub-group exploratory analysis of patients with a wild type EGFR, revealed addition of sorafinib to erlotinib to increase OS and PFS in a randomized phase II study (34). Further work is required for identification and validation of biomarkers predictive of survival benefit from anti-angiogenic agents.

To conclude, the recently reported results of the NExUS trial should prompt the clinical cancer research community to refine our insight into the molecular mechanisms at play in cancer angiogenesis and its inhibition. The required information should arise from correlative studies of human cancer specimens, to assure clinical relevance. Deeper understanding is a requisite for the inhibition of the correct targets, for choosing the right schedule of treatments and for combining the drugs that would produce synergistic tumor-inhibitory effects. Validated predictive biomarkers are urgently required in order to prevent unnecessary exposure of patients to ineffective drugs and to treat the patients most likely to respond to those treatments. Promising advances are being made in these directions, and continued efforts are required in order to derive benefit for our patients.

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