Fibroblastic Growth Factor Pathway

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Recent advances in the therapeutic approach to the treatment of advanced non-small cell lung cancer (NSCLC) have included the use of antiangiogenic agents, which target various aspects of the vascular endothelial growth factor (VEGF) pathway. The pivotal trial evaluated bevacizumab in combination with carboplatin/paclitaxel (CbP) compared with CbP alone.[1] In that trial, bevacizumab added to CbP leads to improved response rates and improved progression-free and overall survival. Although certain toxicities were also increased, for the appropriate patient, the potential benefit of bevacizumab does outweigh its risk. Further improvements in outcomes will require targeting of pathways important in the pathogenesis of this disease.

Angiogenesis is a complex and a critical process playing a key role in tumor growth. The fibroblastic growth factor (FGF) family comprised a number of mitogenic polypeptides (currently, there are 22 known members) involved in the process of angiogenesis.[2] Together with the four transmembrane tyrosine kinase receptors (FGF receptor [FGFR] 1–4), evidence is accumulating suggesting an autocrine and paracrine role in many solid tumors.[3] FGF 2 (basic FGF) is considered a potent stimulator of angiogenesis binding to FGFR-1. FGF-2 has been shown to exert its effect on endothelial cells in a paracrine fashion as a consequence of secretion by tumor or stromal cells.[4] Evidence also suggests an autocrine role for FGF-2 in endothelial cells.[4,5] These observations make this pathway and its ligands potential therapeutic targets in solid tumors.

Coldren et al.[6] used microarray gene expression profiling to evaluate a number of NSCLC cell lines that were either sensitive or refractory to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs). In NSCLC cell lines relatively insensitive to EGFR TKIs, there was frequent coexpression of FGFs (particularly FGR2 and FGF9) and FGFRs (especially FGFR1 and 2).[7] Specific silencing experiments targeting FGF2 reduced anchorage-independent growth of certain NSCLC cell lines that secrete FGF2 and coexpress FGFR1 and/or FGFR2. RO4383596, a TKI that targets FGFRs inhibited FGFR activity and proliferation and anchorage-independent growth of NSCLC cell lines that coexpress FGF2 or FGF9 and FGFRs. In contrast, RO4383596 did not influence signal transduction or growth in NSCLC cell lines lacking FGFs or FGFR2 expression. Taken together, these two reports[6,7] suggest that FGF2 and 9 and their respective FGFRs may represent an autocrine growth loop that is active in EGFR-insensitive NSCLC cell lines.

SUMMARY OF PRESENTATIONS

Brivanib is a small molecule tyrosine kinase inhibitor of both VEGF and FGF signaling. It has shown antitumor activity in lung, breast, and colon cancer xenograft models.[8] Many tumors express elevated levels of FGF-2, which seems to be associated with a poor prognosis in NSCLC and other solid tumors.[8] Brivanib has been shown to effectively inhibit FGF-stimulated and FGF-dependent tumor and endothelial cell lines.[8] In a phase I trial, doses of brivanib of 180 to 1000 mg were studied in previously treated patients with cancer (predominantly colorectal) with no prior exposure to antiangiogenic agents.[9] The maximum tolerated dose (MTD) was 800 mg daily with the most common toxicities consisting of hypertension, fatigue, dizziness, and elevated AST/ALT. Antitumor activity was observed with two patients having confirmed partial responses. There seemed to be an association with FGF-2 expression and the activity of brivanib, but this observation was based on a relatively small number of patients. A randomized discontinuation study is ongoing in multiple tumor types attempting to test the hypothesis that tissue FGF-2 expression may predict responsiveness to brivanib.

TKI258 is a small molecule inhibitor of multiple receptor kinases including the FGFR1 to 3 and VEGF receptor-2. This agent has shown antiproliferative effects in multiple cell lines, which are driven by its target kinases.[10,11] TKI258 has been evaluated in at least 142 patients in both phase I and II clinical trials. The maximum tolerated dose seems to be 500 mg on an intermittent schedule of 5 days on and 2 days off. Dose-limiting toxicities in these trials consisted of fatigue, hypertension and bradycardia; diarrhea, vomiting, and fatigue, which seem to be the most frequent adverse events reported. The clinical development of TKI258 has focused on indications with FGFR gene mutation, amplification, and/or protein overexpression such as the t(4:14) translocation in multiple myeloma, FGFR-3 mutations in urothelial cancers, and FGFR-1 amplification in breast cancer.

Tyro-3, Axl, and Mer share identical domain structure and comprise the TAM receptor tyrosine kinases. TAM signaling leads to angiogenesis, invasion, and enhanced metastatic potential and evasion of apoptosis.[12] TAM receptor

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and ligand expression are clearly seen in NSCLC and correlates with NSCLC cell invasiveness in vitro.[13] Inhibition of TAM receptors has been shown to increase sensitivity of both leukemia and astrocytoma cells in vitro. This suggests the TAM receptor may play a role in the mediation of chemoresistance.[12] Early studies are ongoing in NSCLC.

SUMMARY

FGFs and FGFRs are potentially important targets in NSCLC and other solid tumors. Well-designed clinical trials that incorporate tumor-based correlative analyses interrogating the details of this pathway (overexpression of target or ligand, receptor amplification, and/or mutation) in individual patients are warranted based on the data summarized above. Both single-agent use and combinations of anti-FGFs and/or FGFR inhibitors with standard chemotherapy regimens and other targeted therapies should be pursued.

REFERENCES

1. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 2006;355: 2542–2550.
2. Fischer H, Taylor N, Allerstorfer S, et al. Fibroblast growth factor receptor-mediated signals contribute to the malignant phenotype of non-small cell lung cancer cells: therapeutic implications and synergism with epidermal growth factor receptor inhibition. *Mol Cancer Ther* 2008;7:3408–3419.
3. Jeffers M, LaRochelle WJ, Lichenstein HS. Fibroblast growth factors in cancer: therapeutic possibilities. *Expert Opin Ther Targets* 2002;6:469–482.
4. Donnem T, Al-Shibli K, Al-Saad S, Busund LT, Bremnes RM. Prognostic impact of fibroblast growth factor 2 in non-small cell lung cancer: coexpression with VEGFR-3 and PDGF-B predicts poor survival. *J Thorac Oncol* 2009;4:578–585.
5. Gualandris A, Rusnati M, Belleri M, et al. Basic fibroblast growth factor overexpression in endothelial cells: an autocrine mechanism for angiogenesis and angioproliferative diseases. *Cell Growth Differ* 1996;7:147–160.
6. Coldren CD, Helfrich BA, Witta SE, et al. Baseline gene expression predicts sensitivity to gefitinib in non-small cell lung cancer cell lines. *Mol Cancer Res* 2006;4:521–528.
7. Marek L, Ware KE, Fritzsche A, et al. Fibroblast growth factor (FGF) and FGF receptor-mediated autocrine signaling in non-small-cell lung cancer cells. *Mol Pharmacol* 2009;75:196–207.
8. Ayers M, Fargnoli J, Lewin A, Wu Q, Platero JS. Discovery and validation of biomarkers that respond to treatment with brivanib alaninate, a small-molecule VEGFR-2/FGFR-1 antagonist. *Cancer Res* 2007; 67:6899–6906.
9. Jonker DJ, Rosen LS, Sawyer M, et al. A phase I study of BMS-582664 (brivanib alaninate), an oral dual inhibitor of VEGFR and FGFR tyrosine kinases, in patients with advanced/metastatic solid tumors: safety, pharmacokinetic (PK), and pharmacodynamic (PD) findings. *J Clin Oncol* 2007;25:3559.
10. Lopes de Menezes DE, Peng J, et al. CHIR-258: a potent inhibitor of FLT3 kinase in experimental tumor xenograft models of human acute myelogenous leukemia. *Clin Cancer Res* 2005;11:5281–5291.
11. Trudel S, Li ZH, Wei E, et al. CHIR-258, a novel, multitargeted tyrosine kinase inhibitor for the potential treatment of t(4;14) multiple myeloma. *Blood* 2005;105:2941–2948.
12. Linger RM, Keating AK, Earp HS, Graham DK. TAM receptor tyrosine kinases: biologic functions, signaling, and potential therapeutic targeting in human cancer. *Adv Cancer Res* 2008;100:35–83.
13. Shieh YS, Lai CY, Kao YR, et al. Expression of axl in lung adenocarcinoma and correlation with tumor progression. *Neoplasia* 2005;7: 1058–1064.

