New Strategies in Squamous Cell Carcinoma of the Lung: Identification of Tumor Drivers to Personalize Therapy

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Abstract

Treatment for non–small cell lung cancer has been improving, with personalized treatment increasingly becoming a reality in the clinic. Unfortunately, these advances have largely been confined to the treatment of adenocarcinomas. Treatment options for squamous cell carcinoma (SCC) of the lung have lagged behind, partly because of a lack of understanding of the oncogenes driving SCC. Cytotoxic chemotherapy continues to be the only treatment option for many of our patients, and no genetic tests are clinically useful for patients with SCC. Recent advances in basic science have identified mutations and alterations in protein expression frequently found in SCCs, and clinical trials are ongoing to target these changes. Clin Cancer Res; 18(11); 1–6. ©2012 AACR.

Background

Squamous cell carcinoma (SCC) accounts for about 30% of new cases of lung cancer in the United States. The patterns of incidence have changed over the decades as SCC has become less common, although it is still estimated to account for about 40,000 deaths annually in the United States (1). This reduction is thought to be due to decreased smoking rates as well as changes in the content of cigarettes. Until recently, SCC and adenocarcinoma had very similar overall survival; more recent analyses have shown that outcomes for metastatic adenocarcinoma are improved compared with patients with metastatic SCC (2), possibly due to new treatment options for adenocarcinoma.

For patients with localized or regional disease, treatment options differ very little between SCC and other subtypes of non–small cell lung cancer (NSCLC). Patients without involvement of mediastinal lymph nodes should undergo surgical evaluation, with consideration for adjuvant chemotherapy after resection (3). Patients with locally advanced disease, stage IIIA or IIIB, should be treated with multimodality therapy, often incorporating chemotherapy and radiation with or without surgery. These decisions, for the most part, are made without regard to histology.

Unfortunately, many patients with NSCLC present with metastatic disease or develop metastatic disease following local treatment. The past decade has seen a number of improvements in the treatment of metastatic NSCLC. For patients with EGF receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) translocations, targeted therapies now represent standard front-line therapy (4, 5). A modern cytotoxic agent, pemetrexed, is used in the first-line (6), second-line (7), and maintenance (8) settings for patients with nonsquamous NSCLC. Bevacizumab, a monoclonal antibody against the VEGF receptor (VEGFR), can prolong survival when added to chemotherapy (9). Unfortunately, all of these advances are more effective for patients with nonsquamous NSCLC. EGFR mutations and ALK translocations are not commonly found in patients with SCC, and bevacizumab is associated with an unacceptable risk of pulmonary hemorrhage (10). Pemetrexed is not effective in patients with SCC (6–8) and should not be used for these patients. Thus far, the only targeted agent approved for use in SCC of the lung is erlotinib, which has modest activity in patients with previously treated disease (11).

For patients with SCC, the standard of care is still cytotoxic chemotherapy. Standard front-line chemotherapy consists of a platinum-based doublet (12), and second-line therapy is often docetaxel (13) or erlotinib (11). Recent data indicate that similar to adenocarcinomas, SCCs are clinically, histologically, and molecularly heterogeneous tumors. For patients with SCC, research is ongoing to identify driver mutations (see Fig. 1) as well as targeted agents, including profiling and sequencing studies conducted as part of the Cancer Genome Atlas project (US National Cancer Institute). This article discusses some of the recent discoveries in the genetics of SCC as well as the direction of current and future research.

On the Horizon

Cytotoxic chemotherapy

Although much ongoing clinical research in lung cancer focuses on targeted agents, cytotoxic chemotherapy may play an important role in improving treatment. Paclitaxel is a frequently used drug in NSCLC treatment, but difficulties...
with administration include poor solubility and frequent reactions to the solvent used (cremaphor). To avoid some of these issues, nanoparticle albumin-bound paclitaxel (nab-paclitaxel) was created. Some preclinical evidence also shows that albumin may increase drug delivery to tumors, possibly by interacting with secreted protein, acidic and rich in cysteine (SPARC; refs. 14, 15). In a randomized phase III trial in women with breast cancer, nab-paclitaxel showed higher response rates and longer time to progression than solvent-based paclitaxel (16). Phase II trials of nab-paclitaxel in lung cancer as monotherapy (17) and in combination with carboplatin (18) have shown response rates as high as 39%. A phase III trial randomizing patients with NSCLC to carboplatin/nab-paclitaxel or carboplatin/paclitaxel showed a significantly higher response rate in the nab-paclitaxel arm (33% vs. 25%; P = 0.005). Preliminary estimates of progression-free survival were similar between the 2 arms (19). Several ongoing phase II trials combining carboplatin with nab-paclitaxel (NCT00729612 and NCT01236706) will study a variety of biomarkers, including SPARC, caveolin-1, and serum microRNAs.

**EGF receptor**

EGFR is expressed only at low levels in normal lung tissue, but it is overexpressed in preneoplasia and in many SCCs (20). Erlotinib, a small-molecule EGFR inhibitor, has been approved for use in NSCLC (including SCC) in maintenance therapy (21) and in previously treated disease (11), but benefits are modest and similar to those of cytotoxic therapy (22), with response rates less than 10%. Gefitinib, another EGFR tyrosine kinase inhibitor, seems to have similar activity to erlotinib, although it is not currently available in the United States (4, 22). EGFR mutations in the tyrosine kinase domain that confer sensitivity to gefitinib and erlotinib are found in a significant percentage of adenocarcinomas (23–25). These activating EGFR mutations have also been described in several patients with SCC (24, 26), but it has been hypothesized that these patients have incompletely sampled adenosquamous carcinoma rather than pure SCC (27). About 5% of SCCs have a deletion in the extracellular domain of EGFR (variant III EGFR mutation), but these mutations confer resistance to EGFR inhibitors in *in vitro* studies (28).

Cetuximab is a monoclonal antibody against EGFR and has proven efficacy in SCC of the head and neck (29, 30). In the FLEX study, patients with metastatic NSCLC received cisplatin and vinorelbine with or without cetuximab. Survival was significantly longer in the group receiving cetuximab (11.3 months vs. 10.1 months; P = 0.044; ref. 31). This trial enrolled all histologies of NSCLC, and on subgroup analysis, both patients with SCC and adenocarcinoma experienced benefit from the addition of cetuximab. A Southwest Oncology Group Study, SWOG 0819, is currently accruing patients to receive carboplatin and paclitaxel with or without cetuximab. Patients who are eligible (i.e., nonsquamous histologies) can also receive bevacizumab at the clinician’s discretion. Overall survival is a primary endpoint, and other objectives include the prospective study of EGFR copy number by FISH as a predictive marker for progression-free survival, as well as a variety of other EGFR-related biomarkers, including KRAS and EGFR mutations.

**Insulin-like growth factor-I receptor**

Insulin-like growth factor-I receptor (IGF-IR) is a cell-surface receptor with an intracellular tyrosine kinase domain. Binding of its ligand, IGF-I or IGF-II, activates the kinase domain and stimulates downstream signaling, including the phosphoinositide 3-kinase (PI3K)/Akt/mTOR pathway and the RAF/mitogen-activated protein kinase (MAPK) pathway, promoting cell proliferation and survival (32). IGF-IR plays an important role in carcinogenesis, contributing to cell growth, cell division, and protection from apoptosis. Aberrant IGF-IR signaling has been seen in many tumor types (33), and alterations in this pathway predict poor prognosis in early-stage lung cancers (34).

A randomized phase II trial randomizing patients to carboplatin and paclitaxel with or without figitumumab, an anti-IGF-IR monoclonal antibody, had promising...
results, with response seen in 78% of the patients with SCC treated with figitumumab (Pfizer; ref. 35). Unfortunately, a phase III registration trial was recently closed for futility, with a concern for an increased risk of early death (36).

Small-molecule IGF-IR inhibitors are also being actively studied. It is hoped that these agents have efficacy without some of the toxicities of anti-IGF-IR antibodies. In a phase II study (NCT01186861), erlotinib with or without OSI-906 (Astellas), an inhibitor of IGF-IR and the insulin receptor, is being studied in the maintenance setting in all histologic types of NSCLC. The primary endpoint is progression-free survival. Biomarker analyses, including analysis of the epithelial marker E-cadherin, will also be done.

**Fibroblast growth factor receptor**

The 4 members of the fibroblast growth factor receptor (FGFR) family have important roles in the regulation of cell proliferation and survival (37). Mutations in these receptors have been described in other malignancies (38). In SCC, amplification of FGFR1 has been seen in more than 20% of SCCs but only rarely in adenocarcinoma (39, 40). In preclinical models, small-molecule inhibitors of this receptor can cause decreased cell growth in both cell lines and xenograft models (39, 40). A phase III study (NCT00805194) combining docetaxel with BIBF 1120 (Boehringer Ingelheim), a tyrosine kinase inhibitor with activity against FGFR, platelet-derived growth factor receptor (PDGFR), and VEGFR, recently completed accrual, and an ongoing European phase I and II study (NCT01346540) is enrolling patients with SCC to receive cisplatin and gemcitabine with or without BIBF 1120. Other inhibitors in this class are also in early-phase development, including BGJ398 (Novartis), AZD4547 (AstraZeneca), and dovitinib (Novartis).

**Discoid domain receptor 2 kinase**

Discoid domain receptor 2 (DDR2) is a kinase that interacts with collagen and has roles in cell adhesion and proliferation (41). Mutations have been described in lung cancer and can be found in about 4% of SCCs (42, 43). In cell line and xenograft models, growth of DDR2 mutant cells is inhibited by dasatinib, a tyrosine kinase inhibitor already in widespread use for the treatment of chronic myelogenous leukemia (42). In a clinical trial combining dasatinib with erlotinib, a patient with SCC who responded to treatment was found to have a DDR2 mutation (42). An ongoing single-arm phase II trial (NCT01491633) treats patients with SCC with dasatinib; DDR2 mutations are not required for enrollment, but all patients will be tested. Another phase II trial opening soon (NCT01514864) will enroll a molecularly selected group of patients, including patients with SCC and DDR2 mutations.

**Phosphoinositide 3-kinase**

PI3Ks have crucial roles in cell survival, growth, and motility. This pathway is downstream of multiple other proteins involved in NSCLC, such as B-raf, K-ras, and EGFR. The PI3K CA gene mutation (PI3KCA) gene encodes the catalytic domain of one of these kinases and is one of the most frequently mutated genes in human cancer, including frequent mutations in breast and gastric cancer (44). Mutations in PI3KCA have been described in about 3% of SCCs; copy number gains are present in about a third of tumors (45). These changes are found less frequently in adenocarcinomas. Knockdown of PIK3CA in cell lines with mutations or copy number gains inhibited growth (45). PI3K inhibitors have shown activity against lung cancer in vitro (46), and multiple agents targeting this kinase are in development. For patients with previously treated SCC, a phase II trial randomizing patients to docetaxel or PI3K inhibitor BKM120 (Novartis) is currently accruing (NCT1297491); those patients with previously untreated SCC are eligible for a randomized phase II trial of carboplatin and paclitaxel with or without GDC-0941 (Genentech), another PI3K inhibitor (NCT01493843). Other inhibitors of this pathway in development include BEZ-235 (Novartis), PX-866 (Oncothyreon), and BAY 80-6946 (Bayer).

**AKT1/protein kinase B**

The AKT1 gene encodes protein kinase B, which helps to mediate PI3K signaling. The E17K missense mutation in this gene causes increased activation of the PI3K pathway (47, 48). These mutations are found in 1% to 7% of SCCs and are not found in adenocarcinomas (27, 47, 49). MK-2066 (Merck), an Akt inhibitor, is currently being studied in several phase II trials. In one trial, patients with NSCLC and PIK3CA, AKT, or PTEN mutations will receive MK-2066 as a single agent (NCT01306045). In the BATTLE-2 trial (NCT01248247), patients with NSCLC will undergo biopsy prior to randomization to 1 of 4 targeted therapy arms. One arm includes MK-2066 in combination with erlotinib; another combines MK-2066 with AZD6244 (AstraZeneca), a MAP–extracellular signal-regulated kinase (ERK) kinase (MEK) inhibitor. This combination is also being studied in other malignancies, including melanoma (NCT01519427).

**Platelet-derived growth factor receptors**

The PDGFs are a family of molecules that bind to PDGFRs and have an important role in angiogenesis (50). Multiple studies have shown that higher levels of these growth factors in tumor cells predict negative outcomes in resected NSCLC, including SCC (51–53). A number of agents currently in clinic use for other diseases, for example, sorafenib, sunitinib, and imatinib, inhibit PDGFR. Sorafenib, a multi-tyrosine kinase inhibitor targeting PDGFR-β, VEGF, c-KIT, and B-ras, was studied in combination with carboplatin and paclitaxel in a placebo-controlled phase III trial. Unfortunately, patients with SCC had an increased risk of mortality when treated with sorafenib, carboplatin, and paclitaxel compared with patients treated with carboplatin and paclitaxel alone (54). Another trial investigating a similar inhibitor, motesanib, in combination with chemotherapy, had to limit accrual to only patients with nonsquamous histology after an interim analysis revealed an increased risk of hemoptysis in patients with SCC (55). Because of the concern for increased toxicity with PDGFR inhibitors in
SCC, further trials of these medications should be viewed with caution. Two anti-PDGFR antibodies are currently in development for NSCLC. MEDI-575 (MedImmune) is currently being studied in combination with carboplatin and paclitaxel in NSCLC in a phase I and II trial (NCT01268059). Another phase II trial (NCT00918203) combines IMC-3G3 (ImClone) with carboplatin and paclitaxel. X-82 (Tyrogenex), a VEGFR/PDGFR inhibitor, is currently in phase I testing (NCT01296581).

SOX2

SOX2 is a transcription factor that has important roles in embryogenesis and stem cell maintenance. The SOX2 gene is amplified in about 20% of SCCs, and amplification is associated with higher SOX2 expression (56–59). Amplification may be an early event in carcinogenesis (60). Amplification and overexpression are found much less frequently in adenocarcinomas (56, 58). Studies suggest that higher SOX2 expression is associated with better prognosis in SCC (58).

Conclusions

SCC of the lung is a growing area of interest in terms of molecular diagnostics and treatment options. Recent research has identified several potential driver oncogenes (Fig. 2; Table 1). Although many of these mutations affect only a small portion of patients with SCC, identifying them and using appropriate targeted agents could lead to significantly improved outcomes, as has been shown in patients with adenocarcinoma and EGFR mutations or ALK rearrangements. For example, dasatinib, when used in an unselected group of patients with NSCLC, does not seem to be particularly active (61); however, in a group of patients with DDR2 mutations, this drug may prove to be more effective. Future clinical trials should incorporate biomarker analyses for all patients. Patients with certain molecular abnormalities, including DDR2 mutations, PI3KCA mutations, FGFR1 amplifications, and AKT1 mutations, should be enrolled onto appropriate clinical trials. Through this personalization of care, we hope to improve outcomes for patients with SCC.
Disclosure of Potential Conflicts of Interest

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