Bronchioloalveolar carcinoma (BAC) is a unique subtype of lung adenocarcinoma that has received increasing attention in recent years. Levy and colleagues have provided a comprehensive review of the clinical and pathologic characteristics of this disease, as well as the clinical evidence available to guide treatment of patients with BAC.

Although the World Health Organization defines BAC as a distinct entity, it is now clear that BAC in fact represents a heterogeneous group of diseases with shared pathologic characteristics but distinct molecular aberrations and varying clinical courses and outcomes. Historically, studies have lumped all adenocarcinomas with lepidic growth patterns into the same category, including both pure BAC, which grows along alveolar septa with no evidence of vascular, lymphatic, or pleural invasion, as well as mixed adenocarcinoma with BAC features.[1] Pure BAC, which represents less than 5% of adenocarcinomas, has been shown to have a very low risk of lymph node or distant metastasis,[2] and in fact represents carcinoma in situ rather than true invasive cancer. In contrast, the much more common mixed adenocarcinomas with BAC features are true invasive cancers; their prognosis is similar to or perhaps slightly better than that of typical non–small-cell lung cancer (NSCLC).[3] “Pure” BAC can be further subdivided into mucinous and nonmucinous subtypes; these subtypes have distinct cells of origin, different immunohistochemical staining patterns, and significantly different clinical characteristics.[4]

Molecular Testing Defines Different BAC Phenotypes

Despite shared pathologic characteristics, molecular testing has uncovered distinct oncogenic pathways that differentiate subsets of BAC. For example, the majority of mucinous BACs have mutations in the K-ras oncogene,[5,6] which are commonly associated with tobacco smoking. There is evidence that atypical adenomatous hyperplasia, a premalignant condition, shares many of these same molecular abnormalities and may be a precursor lesion to mucinous BAC.[7] Mucinous BAC is also infrequently associated with p53 mutations, which are common in invasive adenocarcinomas of the lung.[8,9] One particularly interesting concept in BAC biology is the viral oncogene hypothesis, which proposes that some BACs may have an underlying viral cause. The hypothesis is based on the striking resemblance between mucinous BAC and sheep pulmonary adenomatosis, a malignancy caused by the Jaagsiekte sheep retrovirus.[10] So far, however, there is no evidence that a retrovirus is the initiating agent in human BAC.

In contrast, a relatively high rate of activating EGFR mutations have been observed in nonmucinous BAC, although it is unclear whether the BAC classification is a stronger predictor of EGFR mutation than clinical characteristics such as never-smoking status and female sex. However, EGFR mutations are found in only 30% to 50% of nonmucinous BACs, which is just slightly higher than the incidence of K-ras mutations in these lesions (14% to 23%).[5,6] Because EGFR and K-ras mutations are both believed to be oncogenic drivers, and because the two mutations tend to be mutually exclusive, it is clear that pathologic classification alone is an inadequate basis on which to select patients for targeted therapies.

BAC-Specific Clinical Trials and Treatment Recommendations

There have been a number of phase II clinical trials testing either chemotherapy or EGFR inhibitors in patients with advanced BAC; these are well summarized in the review by Levy and colleagues. The authors correctly emphasize that these BAC-specific trials have included a heterogeneous mixture of mucinous BAC, nonmucinous BAC, and adenocarcinomas with BAC features;[11] the heterogeneity of
the lesions in trial participants has complicated interpretation of the results. There have been only two small prospective chemotherapy trials in patients with BAC; both have tested a single agent—paclitaxel—in advanced BAC, with response rates ranging from 11% to 14%.[12,13] There have been no trials testing standard platinum doublet chemotherapy in patients with advanced BAC; thus, doublet chemotherapy should remain the standard treatment in this population, outside of a clinical trial. In addition, a number of trials have tested anti-EGFR therapies in advanced BAC; agents used have included erlotinib,[14] gefitinib,[1] and cetuximab.[15] The trials utilizing EGFR tyrosine kinase inhibitors (TKIs) have shown overall response rates (ORRs) ranging from 12% to 22%; these values are higher than would be expected in an unselected sample of NSCLC patients. However, responses were also associated with other clinical indicators that are predictive of EGFR mutations, such as never-smoking status and female sex; these associations suggest that the elevated ORRs merely reflect the higher incidence of EGFR mutations in this population. As we have seen from recent prospective trials comparing gefitinib with chemotherapy in the first-line treatment of advanced NSCLC, patients with wild-type EGFR have inferior ORR and progression-free survival when treated with EGFR TKIs as opposed to chemotherapy, even in the presence of favorable clinical characteristics.[16] Thus, it is recommended that only patients with documented EGFR mutations receive a TKI as first-line treatment, while patients with wild-type EGFR and those of unknown status should receive standard platinum doublet chemotherapy. Cetuximab does appear to have some activity in this population; however, until further studies are done, it is not clear what role this agent should have in the treatment armamentarium. Despite the traditional practice of including all patients with BAC features together, molecular testing has clearly shown that what we have previously called “BAC” is in fact a mixture of diseases with differing clinical behavior and responsiveness to treatment. We are in complete agreement with Levy and colleagues that future prospective studies of treatment for advanced BAC should be based on molecular markers rather than on clinical or pathologic characteristics.

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