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**Advances in Lung Cancer**

**Management of Bronchoalveolar Carcinoma: An Expert Interview With Vincent A. Miller, MD**

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**Editor's note:**

*Bronchoalveolar carcinoma (BAC)* comprises only a small percentage of non-small-cell lung cancer (NSCLC) adenocarcinomas, but its unique characteristics have enabled researchers to identify improved therapeutic strategies for BAC patients over the past few years. To gain some perspective on how these strategies have affected outcomes, Medscape spoke with Vincent A. Miller, MD, Associate Professor of Medicine at Memorial Sloan-Kettering Cancer Center in New York.

**Medscape: Why has BAC been studied separately from other subtypes of NSCLC?**

**Dr. Miller:** BAC has long intrigued both internists and oncologists because it seems to have unique epidemiologic, pathologic, and clinical features compared with other NSCLC subtypes. For example, although it is smoking-related, its relationship with smoking is less strong than with other types of NSCLC. Whereas over 90% of patients in the United States who get lung cancer are smokers, for BAC, about one third were never smokers. In addition, BAC tends to be more inclined to stay within the lung and is less likely to spread to other organs. There are also some unique radiographic features -- it's often called the "masquerader" because its presentation may be confused with pneumonia or other inflammatory conditions in the lung, and only after a patient fails to improve after a course of antibiotics does one entertain a diagnosis of BAC.

It seems to have a better prognosis when matched stage for stage with other NSCLCs, so a patient with stage I BAC will live longer than a patient with stage I squamous cell carcinoma, even when controlling for factors such as age and gender. In the setting of advanced disease, there's a widely held belief that BAC is less responsive to cytotoxic chemotherapy, although that's not necessarily borne out by the available literature.

These features and characteristics are mostly descriptive because there have not been any randomized trials conducted in these patients. BAC in its "pure" form represents only 2% to 3% of all NSCLCs, making it a relatively rare entity, so accruing patients to prospective trials is difficult. However, what we've noticed is that there are many adenocarcinomas that contain pathologic features of BAC, and these tumors, even if they are mostly adenocarcinomas, behave more like BAC. So a working definition for oncologists may be a much broader population than the rigorous definition that BAC would imply. If one uses this clinically driven classification and includes adenocarcinomas with BAC features with the pure BACs, then it can be a rather common entity; some pathologists have estimated that there's some BAC in almost half of the adenocarcinomas in the United States.

**Medscape: How do the adenocarcinomas with BAC features differ from the pure BACs in terms of pathologic features and smoking history?**
Dr. Miller: Although they're adenocarcinomas, invasive tumors, they're mixed with areas of lepidic growth, which respect the normal anatomic boundaries and grow along the alveoli. About 25% of these patients are never smokers.

Medscape: You noted that there's a belief, not necessarily supported by the literature, that BAC tumors are less sensitive to cytotoxic chemotherapies. Can you elaborate on that?

Dr. Miller: Because of the relatively small population of patients with pure BAC, a lack of prospective trials of BAC, and the fact that most patients with adenocarcinomas with BAC features are classified as adenocarcinomas, it's difficult to determine true response rates. If you look at the small subset of BAC patients in ECOG 1594,[1] the response to chemotherapy appeared lower -- 5% response vs 25% response for the trial overall -- but the median survival was longer, which is supported by a number of retrospective analyses.[2]

There are few prospective trials in BAC. One looked at a 96-hour infusion of paclitaxel[3] and showed a response rate of 14% and a median survival of 1 year. A 14% response for a single agent in a cooperative group setting is pretty comparable to what you would expect for cytotoxic therapy. So there is no unequivocal evidence that it's less chemosensitive, but there is definitely a different natural history from the average NSCLC.

Medscape: What was the impetus to start looking beyond cytotoxic chemotherapies to the targeted therapies?

Dr. Miller: Looking at the gefitinib data,[4] there were a number of clinical characteristics that differentiated patients who responded -- they tended to be female, have adenocarcinoma or BAC, and have negligible or no smoking history. That led a number of researchers to want to study these agents more carefully in BAC.[5] Also, because the disease has a longer natural history that might be less responsive to chemotherapy, it might make sense to find a kinder, gentler way to treat these patients.

The other motivating factor was that if we could pull together a group of more sensitive patients and study them, we might be able to uncover the molecular basis of this sensitivity. Because this is a disease entity less associated with smoking, it might be easier to characterize 3 or 4 different phenotypes within BAC that can be treated in different ways, and one of those can be with an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor.

We're anticipating that the response rate will roughly correlate with the percentage of patients who have the EGFR mutation, which, in the erlotinib study, was about 25%.[6] Of course, there are some patients who regress but have no mutation, and others who have the mutation but do not fit formal RECIST criteria for response.

Medscape: How do you see the availability of targeted therapies such as erlotinib changing the therapeutic landscape?

Dr. Miller: From what we've seen, the drug is clearly active with meaningful and durable responses in about 25% of patients, induces stable disease for a protracted period of time in other patients, and, like with cytotoxics, there is a subset of patients for whom the therapy is not effective and who need to move on to other options.

There is a greater likelihood of response for never smokers or those with negligible smoking history, so based on clinical presentation alone, there are some patients about whom we can be relatively confident that they'll respond. Some former smokers appear to be very sensitive to these drugs as well, and we're trying to develop a model to predict, based on smoking history, the likelihood of sensitivity to these drugs.

I think BAC can serve as a paradigm for understanding lung cancer better because it's a little "cleaner," with less tobacco-related damage. I see us getting a better handle on the molecular biology of the disease, figuring out a strategy for patients with EGFR mutations, vs those with K-ras mutations, vs those who have neither mutation, and hopefully leading to much better outcomes and much gentler treatments.

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References


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