

The ABCs of BAC

Howard (Jack) West, MD
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Hello and welcome to the GRACE video presentation on the ABCs of BAC, Bronchioloalveolar Carcinoma. My name is Dr. Jack West, and I'm a medical oncologist and the Medical Director of the Thoracic Oncology Program at Swedish Cancer Institute in Seattle, Washington. I also serve as the President and CEO of GRACE, the Global Resource for Advancing Cancer Education.

A transcript as well as a PDF file with copies of figures associated with this program are available at www.cancergrace.org/GRACEcasts.

This video presentation is sponsored by the Almquist family. The more we learn about healing cancer today, the better the odds that we, and our children, will triumph over this deadly disease tomorrow.

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Bronchioloalveolar carcinoma is a unique subtype of non-small cell lung cancer that has several distinct features. Under the microscope, an image such as that on the left shows thickened walls of the gas-exchanging sacs in the lungs called alveoli. The classic description of this pattern is *lepidic*, meaning "scale-like." Films show a picture that looks remarkably like pneumonia, as shown on the right, and probably more than any other kind of lung cancer, patients with BAC are routinely diagnosed as having pneumonia for weeks or months before a diagnosis of cancer is actually established.

There are several issues that make BAC of particular interest. Although there is some controversy about this, it is generally felt to be rising in incidence, or at least being recognized and diagnosed more commonly. The pure form of BAC, which has no invasive component, is relatively uncommon, but some component is present along with some element of invasive adenocarcinoma in about 15-20% of cases of non-small cell lung cancer. The demographics of BAC are also unique, in that about 1/3 of patients with BAC are never-smokers, far more than are seen for lung cancer in general, and more women are affected than men, which is a reversal of the trend for other forms of lung cancer.

The classic presentation is also with hazy lung infiltrates, which are sometimes diffuse, and extensive throughout one or both lungs. The pattern of progression of pure BAC is that it spreads within the lungs but does not classically involve lymph nodes or spread elsewhere in the body. This is because it doesn't have an invasive component that can spread into the lymphatic system or blood stream to other locations. In some cases, patients can develop a frothy sputum, known as bronchorrhea, and this can be very copious, even a liter or more per day.

Another important and distinct aspect of BAC is that the rate of progression can be extremely variable. More than any other type of lung cancer I see, BAC can be so slow that it doesn't clearly need any treatment for years, growing at a barely perceptible rate from one year to the next. Other BAC tumors can progress rapidly and lead to declines in a patient's lung capacity and activity level over a matter of just weeks.

An extremely important factor that I previously noted is that what is commonly referred to as BAC is actually part of a spectrum, ranging from the pure form that doesn't have a solid, invasive component, as shown in the upper left, to the more common invasive adenocarcinoma, shown in the lower right. In between are the mixtures of non-invasive BAC with some invasive adenocarcinoma, and these may be predominantly non-invasive and termed BAC with focal invasion or predominantly invasive and termed adenocarcinoma with some BAC features.

The more favorable survival with BAC has been demonstrated for stage I BAC compared with other adenocarcinomas, as shown in a retrospective review out of Massachusetts General Hospital. In some recent series from Asia, the smaller, pure BAC tumors have been associated with a five-year survival actually approaching 100%.

Other work from the same group out of Mass General has shown that the median overall survival of patients with advanced BAC is also significantly longer than that of patients with other subtypes of non-small cell lung cancer.

It generally hasn't been felt that this more prolonged survival has been due to greater responsiveness to chemotherapy. BAC historically hasn't been very well studied, given that it represents such a small proportion of non-small cell lung cancer cases. They have generally been pooled with other subtypes or sometimes excluded from trials, but in neither situation has it been possible to properly assess how BAC patients do with standard chemotherapy. Limited retrospective reviews have generated far-ranging conclusions. As shown in the table on the bottom of this slide, a careful look has shown that the benefit may be comparable between BAC and non-BAC lung cancer, but many oncologists have historically perceived that BAC is resistant to chemotherapy. This may be because the diffuse, poorly defined lung lesions that typify BAC aren't conducive to measuring tumor shrinkage in the same way as a more solid, circumscribed lung cancer.

But after years of being considered an unusual curiosity in the field of lung cancer, BAC became a source of much greater research focus when it was observed by lung cancer experts at Memorial Sloan Kettering and some other cancer centers that a minority of patients with advanced BAC can have a dramatic and rapid response to the emerging oral agents targeting the epidermal growth factor receptor (EGFR), such as gefitinib (also known as Iressa) and erlotinib (also known as Tarceva). Here you can see patient's chest x-rays taken just 5 days apart and demonstrating the remarkable response obtained with Iressa over that short time.

In addition, these responses could also be very long-lasting, as shown in this pair of CT scans taken two years apart in a patient with widespread BAC. In fact, this particular patient had a mixture of adenocarcinoma and non-invasive BAC, so the impressive responses are not just limited just to patients with the pure form of BAC.

This work led to trials of the EGFR inhibitors in advanced BAC. I led one through the Southwest Oncology Group (SWOG) that administered Iressa at 500 mg per day to patients with advanced BAC or a mixture of adenocarcinoma and BAC. A total of 135 patients with either chemo-naïve or previously treated disease were enrolled, and we saw a response rate of 16% and a median overall survival of 13 months. However, these rather unimpressive results don't really tell the whole story. Up to 30% of patients had prolonged stable disease even if they didn't show a response and significantly better overall survival results were seen in certain groups. Women, never-smokers, patients who developed a rash, and those with a better performance status did particularly well. But some patients did remarkably well, including six patients who continued on Iressa without progression for four years or longer. A look at the clinical and molecular characteristics of these patients showed that not all of these patients were women or never-smokers, nor did they necessarily carry an EGFR mutation or show EGFR gene amplification. In fact, none of these six patients met the criteria for a formal response, but rather they all showed very prolonged non-progression for years, some still ongoing.

A study conducted through Memorial Sloan Kettering looked at a similar population of 101 patients with advanced BAC or adenocarcinoma with BAC features and gave the oral EGFR inhibitor erlotinib, also

known as Tarceva, at the standard dose of 150 mg daily. The response rate and survival were a little better than SWOG saw with Iressa, but what the investigators focused on was the particularly favorable results among patients with an EGFR mutation, who showed a response rate of 83% and a median survival of approximately two years. As shown in the so-called “waterfall plot” that shows tumor shrinkage by a bar going downward from the higher horizontal line, most of the best responses, at the far right, are gray bars that note patients with an EGFR mutation. However, many patients with no mutation, who are shown as orange bars, and even some with K-Ras mutations and shown with blue bars, had good tumor shrinkage or at least stable disease.

This study with Tarceva also showed that responses were more common in never-smokers than in former or current smokers, in women more than men. In addition, responses were only seen in the patients who developed a rash. There was no evidence that the best results were only in treatment-naïve patients, nor was there any suggestion that results were better for patients with pure form of BAC. If anything, the response rate was better in patients with a mixture of BAC and invasive adenocarcinoma, as shown at the bottom of the table.

In the last few years, those of us with a major focus on BAC have come to recognize that the two main subtypes of BAC, known as mucinous and non-mucinous, have many important and clinically relevant differences.

Survival with EGFR inhibitors appears to be best for patients with the non-mucinous BAC or a mixture of adenocarcinoma and BAC, and it's rather poor with patients who have the mucinous subtype of BAC. As shown by the blue bar, a few patients who were felt to have invasive adenocarcinoma and no BAC were actually enrolled by some institutions, highlighting the variability in interpretation of the BAC diagnosis from one center to another.

Though the work assessing differences between BAC subtypes is still preliminary, it appears that the favorable results with EGFR inhibitors are confined to patients with the non-mucinous subtype, and these are more likely to be never-smokers and carry an EGFR mutation. Greater responsiveness to standard chemotherapy agents may be seen in patients with the mucinous BAC subtype, although we have very little evidence to go by here.

Finally, one subtype of BAC that has been particularly troubling is the “pneumonic” form, which is typically a pneumonic BAC that spreads diffusely through one or more lobes and is associated with a copious bronchorrhea. Thus far, it has appeared that this form is likely resistant to EGFR inhibitors and can progress rapidly. We haven't yet found an effective treatment for this sometimes very aggressive BAC variant.

To summarize, BAC is a unique subtype of lung cancer that accounts for about 2-4% of non-small cell lung cancer cases, but it's a component in about 15-20% of patients, in combination with invasive adenocarcinoma. Under the microscope, the pure form is noninvasive and spreads thinly over the walls of air sacs, interrupting gas exchange. On x-rays and CT scans, it typically appears as hazy infiltrates, often described as ground-glass opacities, or else as widespread small nodules within the lung only. The patient population typically includes a higher proportion of never-smokers and women than other lung cancer subtypes.

Among the most intriguing aspects in the study of BAC has been its response to treatment, which can include some of the most dramatic and long-lasting responses we ever see in lung cancer and it occurs consistently in a minority of patients who receive an oral EGFR inhibitor like Tarceva or Iressa. Responses may be more likely in certain patient subgroups and may be especially pronounced in patients with an EGFR mutation. We are also gaining a new understanding that there may be clinically distinct subgroups even within the rather small population of patients with BAC. The non-mucinous subtype may be especially likely to respond to EGFR inhibitors, while pneumonic BAC, which is typically an aggressive mucinous BAC, has been especially difficult to treat effectively.

Nearly everything we know about BAC has been based on research conducted over the last decade, and we continue to learn more with each passing year.

You can find additional details on several of these topics within the subject archives at the web address www.cancerGRACE.org/lung. Members of GRACE can also leave comments and questions about this presentation at the web address in the middle of this slide. Thank you for your interest.