The Variability of Bronchioloalveolar Carcinoma (BAC): Non-Mucinous and Mucinous BAC

One of the themes that we've covered in some of the posts introducing the clinical entity of BAC is the variability in its natural history. In fact, much of what we've been learning about BAC has been in the last several years, and we're still learning more about it all the time. One of the things we've struggled with is the range of outcomes, that some patients can experience rapid deterioration and no response at all to EGFR inhibitors, while other patients can have a remarkably slow progression, and they sometimes will have an astounding regression of disease from EGFR inhibitors. It sometimes seems as if there are at least a couple of diseases being labelled as BAC. In fact, that's the case, and it's been part of the confusion in why some people don't fit a simplified view of what is supposed to happen in BAC. So let's talk about mucinous and non-mucinous BAC.

Non-mucinous BAC is the largest group, accounting for about 40-60% of the patients, while perhaps 30-40% have mucinous BAC, and about 10-15% fall in between and are classified as mixed or indeterminate. In truth, this is pretty high-level classification that is not always (or even often) mentioned in pathology reports of BAC, and I would consider it relatively unreliable if read from a small amount of tissue and/or read by a pathologist without much expertise in lung cancer. In truth, even expert pathologists differ in how they interpret BAC diagnoses. Here's a slide of BAC and adeno subtypes under the microscope:

Mucinous BAC is the subtype that is associated with a cough productive of thick sputum, and it tends to appear more localized and pneumonia-like on CT scans than non-mucinous BAC, which appears most commonly as a buckshot appearance of lots of tiny, diffuse nodules:

There is a pattern, sometimes considered a separate stage, of BAC that is called the pneumatic form, and this is characterized by one lobe being filled throughout with BAC (abstract here). This is a mucinous subtype, and it has been identified as being a particularly
challenging form of BAC. Because it is confined to a single lobe, surgery is sometimes performed, either because that is the only area involved with disease or because the cough is so bad that patients want surgery in order to feel better by removing the affected area of lung. Unfortunately, this pneumonic form typically recurs within just a few months, and our therapies for it like EGFR inhibitors and chemo have been disappointing.

There are some patterns emerging that appear to have relevance to how we treat BAC. EGFR mutations are seen almost exclusively in patients with the non-mucinous form, in which they appear in approximately 20-25% of cases (abstracts here, here, and here). The numbers are higher when testing for gene amplification for EGFR as determined by fluorescence in situ hybridization (FISH), in which 44% of non-mucinous BAC tumors were EGFR FISH-positive, vs. just 4% for mucinous BAC (abstract here). In contrast, K-ras mutations are seen more frequently in resected mucinous compared with non-mucinous BAC (abstract here), and I’ve described previously how the evidence is converging that the tumors with K-ras mutations are highly unlikely to respond to EGFR inhibitors.

In fact, the results with EGFR inhibitors are consistent with what these studies would predict. The response rates of patients with Iressa for advanced BAC (abstract here) actually showed a response rate of 30% and another 40% with stable disease among patients with non-mucinous BAC, vs. no patients with mucinous BAC showing either a response or stable disease, and actually all showing progression as their best response on Iressa (only a subset of patients on the trial had enough tissue for this assessment, so the numbers are small). Another trial using Iressa for BAC also found a higher progression-free survival, disease control at 3 months, and response rate among the patients who had non-mucinous compared with mucinous BAC (abstract here).

On the other hand, in the very limited information we have about chemo for BAC, 19% (3/16) of the patients with mucinous BAC responded to taxol (given over 4 straight days as a slow IV infusion, which has fallen out of favor), compared with no (0/13) patients with non-mucinous BAC (abstract here). There isn’t a lot of information here, but it does suggest that patients with mucinous BAC may be better served by pursuing conventional chemo rather than immediate EGFR inhibitor therapy, which is commonly recommended as first-line treatment now for advanced BAC.

In fact, the ex-smoking woman with the CT images used above to illustrate mucinous BAC came to see me a few months ago, with a very rapid progression over the preceding few weeks to months, in terms of shortness of breath and weight loss. She was declining so quickly we felt a great need to start treatment on her, which was complicated by the fact that she was quite weak and debilitated. I started her on tarceva, because it is now becoming an attractive early standard for BAC, and also because I suspected I’d be able to tell very quickly whether she was responding or not. Also, because the responses to tarceva can be so dramatic and long-lasting, I didn’t want to have her miss the chance to be a major beneficiary of it. However, she didn’t respond, and she continued in that tailspin, as I thought she might, given that this was mucinous and that she had a significant smoking history. Within a very short time I stopped her tarceva (far shorter than I would usually do, but she wouldn’t survive the usual two month test), and I started her on carbo/taxol/avastin. While it hasn’t been miraculous in
terms of response, she definitely came out of her tailspin, gaining weight and now off of oxygen. At this point, I’m not sure if it’s the chemo, the avastin, or the combination, but I’m encouraged to have seen a patient turn around from a startling decline with something other than tarceva. It suggests to me that, along with the small amount of evidence we have from the taxol trial noted above, mucinous BAC may be better served by a chemo-based approach, and perhaps the avastin is a significant help.

The Southwest Oncology Group is just now starting a trial that I’m leading, known as SWOG 0635, that will enroll patients with BAC (mucinous or non-mucinous, also including adenocarcinoma with BAC features) to receive the combination of tarceva and avastin, which we expect will be first-line therapy for most patients. We’ll be looking very closely at differences based on histology. Perhaps the avastin provides a key benefit for patients with mucinous BAC that will lead to better results for this combination than tarceva alone. Perhaps the avastin/tarceva combination will lead to even better results with tarceva for the population with non-mucinous BAC, who already seemed to benefit considerably as a group from EGFR inhibitors alone (as avastin improved outcomes vs. chemo alone for advanced NSCLC in general). For now, we don’t know, but we’re learning more, and much of that is from looking more carefully at what we’ve done and trying to discern patterns that can be lost by pooling the results. It really does look like BAC encompasses more than one disease.