Optimal Systemic Therapy for Bronchioloalveolar Carcinoma (BAC)

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TRANSCRIPT & FIGURES
One of the unusual subtypes of lung cancer is known as bronchioloalveolar carcinoma, or BAC. That is a subgroup of adenocarcinoma, and many clinicians treat it as a special case. Because of that, it’s fair to ask the question of, “what is the best whole body, or systemic, therapy for that setting?” There are some clinicians who will tell patients that standard chemotherapy does not work and shouldn’t be tried at all. There are some people who feel that oral EGFR inhibitors, drugs like Iressa (gefitinib), or Tarceva (erlotinib), or Gilotrif (afatinib), might be the treatment of choice. But those are all oversimplifications based on prior information, and we now know better. In fact, as is often the case, we need to individualize for the particular patient, and their cancer.

The first main question to ask is whether it’s necessary to treat at all. Some patients will have an advanced or metastatic, cancer, but it is not growing at a pace that is really a threat, and for patients who don’t have symptoms, and who might have very slow-growing cancer, there shouldn’t be any rush to start treatment right away, just because they have what is technically called stage 4 cancer. There are patients who can go very long periods of times with no symptoms and feel well for months, or even years.

But, if patients demonstrate clinically significant progression of their disease, and especially if they have symptoms, it’s appropriate to think about what the best whole body, systemic therapy is.
The trial that really changed our prospective on how to approach these patients was called IPASS. This was an Asian study of over 1,200 patients, from Asia, who had a never-smoking history, and an adenocarcinoma. And this group of Asian never-smokers with an adenocarcinoma are the kinds of patients who we have long recognized as being especially likely to respond well to oral EGFR inhibitors. Because of that, this trial directly tested Iressa to standard chemotherapy in a large number of patients who were enriched to likely respond well. However, it did not require that patients have an EGFR mutation, because the story about EGFR mutations was still being developed, and we didn’t know how important that really was – really not until this trial.
The study looked for a significant difference in progression-free survival – the time before the cancers began growing again, after an initial response or stable disease. When we look at the results for progression-free survival in the bottom left part of this slide, you can see that it’s an unusual pattern – it crisscrosses – it’s kind of like a figure eight, and when we see that, it suggests that there’s actually two different populations within the broad group here. The study was designed to look for EGFR mutations in patients where there was tissue available, and they looked at over 400 patients who did have tissue available, and found that 60% of the patients did have an EGFR mutation, which of course means that 40% did not, even though they were Asian never-smokers with an adenocarcinoma, and a group that we might reflexively want to give these oral therapies to.

But, as you can see from the curves shown in the middle and the right side of the bottom portion of the slide, you got completely different results if patients did have an EGFR mutation, versus if they did not. If you did have an EGFR mutation, you did remarkably better getting the oral EGFR inhibitor. On the other hand, if you do not have an EGFR mutation, you did far, far better by getting standard chemotherapy, and we also see this when we look at the response rates.
In fact, when you look at the patients with an EGFR mutation, Iressa was associated with a response rate of 71%; if you didn't have that mutation, your response rate to Iressa was 1%. You were far better served by getting chemotherapy if you don't have an EGFR mutation – you had a response rate of about 23-24%, which is, of course, much better than that 1% with Iressa.

So, this really changed our thinking about the field – we used to, perhaps, think that we could clinically separate patients and say, if you’re Asian, never-smoker, if you have an adenocarcinoma, we can just start by giving you an EGFR inhibitor, and expect that we were serving you well. In fact, this...
showed that if you guessed wrong, you could really do a disservice to the patient. That the patients who don’t have an EGFR mutation should get standard chemotherapy as their first-line treatment, and the same applies to advanced BAC – in patients who don’t have an EGFR mutation, they should go on to get standard chemotherapy, unless they have another driver mutation that we would standardly look for, such as an ALK rearrangement, or possibly a ROS1 rearrangement.

So this is how we now treat advanced BAC – it is individualized based on the molecular characteristics of their cancer. You look for a driver mutation, and if you find one for which we have an oral therapy that tends to work very well, that is your first-line treatment of choice. If you don’t find one of those driver mutations, your first-line treatment of choice is standard chemotherapy based, potentially adding the drug Avastin or bevacizumab, which is an anti-angiogenic agent.
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