Not all EGFR Activating Mutations are Created Equal: Time to Stop Pooling Them Together

It’s been a decade since EGFR gene mutations were first identified as highly correlated with a high probability of response to EGFR tyrosine kinase inhibitors (TKIs) like Iressa (gefitinib) and Tarceva (erlotinib), and more recently Gilotrif (afatinib). We’ve learned that there are an array of EGFR mutations, and that the two most common ones, an exon 19 deletion or an L858R substitution on exon 21 (an exon is a specific expressed portion of a gene), each somewhere around 40-45% of the EGFR mutations seen, are actually the ones consistently associated with a dramatic and often long-lasting response to EGFR TKIs. In contrast, the other 10-12% of EGFR mutations, most commonly on exon 18 or exon 20, are a heterogeneous group with a less clear benefit from EGFR TKIs.

For about the last 5 years, the lung cancer community has reached a pretty clear consensus that the exon 19 deletions and exon 21, L858R substitutions represent so-called “activating mutations”, and patients with these specific mutations in their tumors are the ones that have, in trial after trial, been shown to have a markedly higher response rate (RR) and longer progression-free survival (PFS) with EGFR TKIs than with standard chemotherapy. Over that time, they have been pooled together and largely presumed to be very comparable. More recent research presented at ASCO 2014, however, rekindles questions that go back many years and cast doubt on whether we should really pool these two mutations together.

Back in 2006, two different publications came out — one from Boston’s Dana Farber Cancer Institute (on the top of the figure below), and another from New York’s Memorial Sloan-Kettering Cancer Center (bottom of figure below) — each independently reported that while both mutations were associated with very good responses to Iressa or Tarceva, the exon 19 patients seemed to do better, potentially in terms of both PFS and overall survival (OS).
However, in the years that followed, a smattering of trials suggested better results in exon 19 patients, while others showed no real differences. In fact, I summarized the general thinking about this question of exon 19 deletions vs. exon 21, L858R substitutions back in 2011 in a post here. Essentially, while there might be some differences, the results have been inconsistent, so we have to divide EGFR mutations as “activating mutations” on either exon 19 or 21 for which EGFR TKI therapy is the leading first line treatment of choice, or “rare mutations” for which the value of EGFR TKIs is much less clear. These patients were included on the LUX-Lung 3 and 6 trials, comprising 10-12% of the study population, but they were removed from the survival analysis, almost certainly because they skewed the results in an unfavorable direction — we don’t extrapolate that the consistently favorable results of EGFR TKIs for exon 19 and exon 21 patients applies to those with rare EGFR mutations.

But then, at ASCO 2014, a couple of highlighted presentations clearly indicated that there are two distinct populations within that group with an activating EGFR mutation. One was the Japanese trial by Kato and colleagues of Tarceva alone or with Avastin (bevacizumab) in EGFR mutation-positive patients that I described a couple of weeks ago. This showed that, while those with either common mutation demonstrated a significant benefit from addition of
Avastin, those with an exon 19 deletion had a superior PFS compared to those with an exon 21 L858R mutation whether you're looking at Tarceva alone or the Tarceva/Avastin combination. That study is still too immature to provide any OS results.

The difference between outcomes in exon 19 vs. exon 21 patients was more highlighted in the pooled analysis of the LUX-Lung trials with afatinib that I just reviewed. The survival benefit with first line afatinib was entirely a product of a very significant benefit in those patients with an exon 19 deletion, while those patients with an L858R substitution trended toward a better survival with chemo.

This trend toward an unfavorable survival is a very surprising result after these same patients likely experienced a very striking improvement in RR and PFS for afatinib — though we haven’t yet seen the RR and PFS data presented broken down by mutation subtype, except in this slide provided to me by Dr. Yang, which is remarkably helpful, showing PFS and OS benefit for EGFR TKI or chemo in a wide range of trials as a function of specific mutation:
The figure above, called a *forest plot*, shows greater benefit for one treatment or another by how much each yellow dot shifts from the vertical line. With the white vertical line representing the two treatments leading to equal results, a dot off to the left represents a benefit for EGFR TKI, and a yellow dot to the right represents a benefit for chemotherapy — and the further from the vertical line, the greater the benefit for one strategy vs. another. The horizontal bars on either side of each yellow dot are called error bars, and they capture the variability in the results within the group, so longer horizontal bars represent a lot of variability in the results and therefore less confidence that the yellow dot really belongs where you see it. The full length of the horizontal bars on either side of the dot represent the place where the dot could really belong 95% of the time, and if the horizontal bars cross the vertical white line, the difference is not statistically significant. Finally, the numbers listed under HR, for hazard ratio, is a reflection of the improvement or detrimental effect of EGFR TKI. A HR of 0.35 corresponds to 65% improvement with EGFR TKI vs. chemo, while a HR of 1.35 represents a 35% better result with chemotherapy.

That’s a lot of explanation, so I’ll just summarize what I see as the key points. The various EGFR TKI studies show that all of the EGFR TKIs tested against chemo in EGFR mutation-positive patients showed a clear improvement in PFS, usually with comparable results in exon 19 deletion and L858R mutation patients, but occasionally a less impressive
effect in L858R-positive patients. In contrast, the OS effect always becomes diluted and moves toward less benefit with EGFR TKI, sometimes with overall survival crossing equivalence and having the exon 21 patients on the side more favorable for chemotherapy. This effect was most pronounced for the LUX-Lung 3 and 6 trials with afatinib, for whatever reason.

How can these treatments lead to clear improvement in the early result of PFS, which measures the beneficial effect of the first treatment, and then switch to a trend of harmful effect for OS? The short answer is that we don’t know if this is a real effect. It hasn’t been seen consistently and didn’t reach statistical significance, but it raises the question to me of whether the sequence of therapy may be important. Though we’ve largely presumed that it shouldn’t matter if you give an EGFR TKI or most therapies now or 6 months from now, as long as a patient is still fit enough to tolerate it, we’ve seen hints that this may not be true. For instance, the TORCH trial looked at molecularly unselected patients in Europe (very few of them likely to have an EGFR mutation) and randomized patients to cisplatin/gemcitabine initially, followed by Tarceva at progression or Tarceva initially, followed by cisplatin/gemcitabine at progression (see figure below for visual representation). While we might have suspected that both groups would perform comparably if getting the same drugs over time, the trial was actually terminated early, after a significant survival difference was seen that favored initial chemotherapy:
This result was a key finding that led us to conclude that we don’t want to start someone on an EGFR TKI based on their status as a never-smoker with an adenocarcinoma: if you don’t know someone has an EGFR mutation, they are better served by starting with chemotherapy rather than presuming they have an EGFR mutation. Sequence must matter in ways we don’t yet understand well. Here, it may be that patients with an L858R mutation do less well after they receive an EGFR TKI, or at least afatinib.

It’s important to underscore the variability from one trial to another. The CALGB trial of Tarceva alone vs. combined with carboplatin/paclitaxel chemotherapy included never- or light prior-smoking patients with an advanced lung adenocarcinoma, and a subset of patients were tested and found to have an EGFR mutation. The breakdown of results in the patients with exon 19 vs. exon 21 mutations is shown below and shows a clear, striking difference in RR and PFS with Tarceva or Tarceva/chemo, but survival was just as good in patients with an exon 21 mutation:

I don’t think we can tie up the results of these studies neatly with a tight conclusion. Instead, the findings indicate that we should be more careful about looking at the results of EGFR TKI
therapy trials as separate for the two common mutations. The EGFR TKIs may possibly have different activities in one group or another, sequence may matter quite a bit, and the optimal treatment sequence may be different for patients with an exon 19 deletion vs. an L858R substitution. While efficacy of the EGFR TKIs seems to be most favorable in those patients with an exon 19 deletion, the survival differences are less consistent.

It’s time to back up and question some of the dogma we established over the past 5-6 years. There are actually two distinct populations in that pooled group of patients with activating EGFR mutations.

Do you feel this should change how we manage patients? Should it dampen enthusiasm for EGFR TKIs in those with an L858R mutation?

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