COX-2/EGFR Inhibitor Therapy: Hope or Hype?

While there have been studies of the COX-2 inhibitor celebrex in combination with chemo for treating NSCLC, the palpable buzz about celebrex in treating lung cancer has been from a trial by my friend Karen Reckamp, formerly at UCLA, now recently moved to City of Hope Cancer Center in nearby Duarte, CA. Several studies have shown that EGFR expression is associated with increased cell growth, increased angiogenesis, increased tissue invasion and metastasis, and a worse survival compared with patients who have tumors that don’t overexpress EGFR. And as I wrote in my introductory post on COX-2 inhibition, high expression of this enzyme can also lead to worse patient outcomes among folks with NSCLC (COX-2 actually hasn’t been shown to be expressed significantly in SCLC). In fact, these two pathways interact to regulate cell proliferation, migration, and invasion (reference article here).

This led to the idea that inhibiting both the EGFR and COX-2 pathways together could potentiate apoptosis (programmed cell death, which we want the cancer cells to do), inhibit cancer cell growth, and decrease tumor invasion and metastasis. Dr. Reckamp conducted a trial (abstract here) in which the dose of tarceva was the standard 150 mg by mouth every day, and the dose of celebrex was gradually increased from 200 mg by mouth twice daily to higher and higher levels in order to find the optimal biological dose of celebrex in this combination. This is in contrast to an approach in which investigators assumed that a good dose of celebrex was 400 mg twice daily, based on the research in which this agent effectively reduced colon polyps in patients with a genetic predisposition to develop colon polyps that lead to colon cancer (abstract here). In order to identify an optimal celebrex dose, she and her colleagues monitored urine levels of downstream markers of celebrex activity. She found that the combination of tarceva and celebrex was well tolerated at all of the doses they tested among the 22 patients on the study, right up to celebrex at 800 mg twice daily, with the side effects really being limited to those expected and well described for tarceva, primarily rash and other skin-related side effects, as well as some diarrhea and other GI problems. A single patient developed a GI bleeding. They found that the dose of 600 mg twice daily produced a more effective COX-2 inhibitory effect based on urinary markers than 400 mg twice daily, but 800 mg by mouth twice daily did not add significantly beyond that, so 600 mg twice daily was identified as the optimal biological dose. The excitement about the trial came from the high response rate of 33% (7 of 21 evaluable patients, with one discontinuing the trial after just two weeks because of the FDA warning about potential risk of cardiovascular complications with celebrex, along with other COX-2 inhibitors). These responses have lasted anywhere from 16 to 94 weeks. Another five patients (24%) experienced stable disease as a best response, with a duration ranging from 8 to 76 weeks, for a total disease control rate of 57%. How does this
compare to tarceva alone? In the larger phase III trial BR.21 (abstract here), the response rate was 9% and the rate of stable disease was 35%, for a disease control rate of 44%. She has also been able to look in some detail at the tissue of the patients with a response or stable disease on the celebrex/tarceva combination, and she found that 5 of 11 of those disease control patients with tissue available have a mutation. A total of 7 patients on the trial were never-smokers, of whom 6 had a response or stable disease. Responses and stable disease were also seen not just at the higher doses, but commonly at the doses below the identified optimal biological dose for celebrex of 600 mg twice daily. There’s no doubt that these results are encouraging. The question is whether these results are conclusive enough that they should change our practice so that we now routinely give patients tarceva along with celebrex at 600 mg twice daily. In fact, this isn’t the only experience of combined EGFR and COX-2 inhibition, but the other published trial didn’t generate any buzz, because there wasn’t anything to buzz about. Gadgeel and colleagues from the Karmanos Cancer Institute at Wayne State Univ. in Detroit just published their experience of treating 27 patients with advanced, chemo-pretreated NSCLC with the combination of Iressa at 250 mg daily along with celebrex at 400 mg twice daily (full reference article here). They reported a rather unimpressive response rate of just 7% (2/27 patients), although the investigators did note that a female never-smoking patient had not yet progressed more than three years after enrolling on the trial. However, she actually stopped taking the celebrex after 20 months, and she continues to show a partial response with just the EGFR inhibition after more than three years, so it seems clear to me that the COX-2 inhibitor isn’t driving the benefit in her case. Dr. Gadgeel and his colleagues also studied some preclinical lung cancer cell lines and found that celebrex improved the inhibitory effects of EGFR inhibitors on the cell lines that have an EGFR mutation, but it didn’t add anything to EGFR inhibitors in the cell lines that had normal, non-mutated EGFR (abstract here). At this point, given the mix of results in what at this point is just two small studies, the fact that celebrex can have fatal cardiovascular side effects, and that it isn’t commonly used or especially well studied at the 600 mg twice daily dose that has been defined by Dr. Reckamp as the optimal dose, I wouldn’t recommend it for routine use outside of a clinical trial, but I recognize that this is the conservative stance that many patients don’t want. What can we really expect from the combination? The 7% response rate seen in Detroit, or was that because the dose of celebrex wasn’t high enough or Iressa just isn’t as good a drug as Tarceva, or both? Or can we really expect to see a response rate of 30% or more from the combination of tarceva with celebrex at 600 mg twice daily? Small, single-center phase II trials are notorious for showing unusually great results that are not borne out in larger, multicenter trials (the response rate for the now plain old carbo/taxol combination was reported as over 60% in one of the initial phase II studies of it, but it didn’t exactly deliver on that promise). While I think that Dr. Reckamp and her colleagues are doing great work, I have to question whether the results would be as strong if at least 5 of their better responding patients hadn’t had an EGFR mutation and 7 of their 21 evaluable patients weren’t a never-smoker. This is why we need larger trials to clarify the picture. In fact, a larger randomized phase II trial is being developed by Dr. Reckamp and colleagues, in which tarceva with celebrex 600 mg twice daily is being tested against tarceva with a placebo. This trial is now recruiting, and it’s looking at progression-free survival as the primary endpoint, while looking at overall survival, response rate, and multiple tissue, blood, and urine molecular correlates to see if it’s possible to identify whether the majority of patients or a more limited subset get a greater benefit from tarceva/celebrex in combination than tarceva alone.
I know that there’s a lot of enthusiasm out there about COX-2 inhibitor therapy, especially in combination with tarceva. I’m skeptical about it, but I would love to have this combination turn out to be a real improvement, even for a limited subset of patients. In patients who don’t have a lot of alternatives, and especially the patients who have had a prolonged response or stable disease on tarceva alone, I’d strongly consider adding celebrex to see if the results could be restored/improved with a combination. But right now I’m just committed to seeing what the next trial shows, keeping open-minded about it, but not yet concluding that the combination represents a breakthrough at this point. I don’t know of any experts endorsing this combination as an off-protocol standard approach, including Dr. Reckamp herself. But I’d be interested in hearing whether you agree that it’s appropriate to be cautious or whether I’ve just seen too many TV ads for aggressive lawyers looking for an opportunity to prey on a situation in which something bad happened to someone and now someone needs to pay. The docs who aren’t writing prescriptions for celebrex to everyone with lung cancer aren’t trying to deprive anyone of effective treatment, but rather want to see whether there’s really more compelling evidence that it’s an improvement in a larger group of patients than the very limited numbers we’ve seen so far.