Novel Agents for Lung Cancer: Proteasome Inhibition with Velcade (Bortezomib)

Much of the focus on novel agents has been on strategies like inhibition of the epidermal growth factor receptor (EGFR) that can stimulate tumor growth, or anti-angiogenesis, blocking the tumor blood supply. But there are other, novel therapies that are also being tested in lung cancer as well. One of these is proteosome inhibition, with an agent like Velcade (bortezomib), which is approved for treating the plasma cell (blood) cancer multiple myeloma and also has activity in lymphomas.

Sometimes referred to as the “cellular housekeeper”, proteasomes are a set of proteins that are inside the nucleus of the cell and regulate the concentrations of multiple important regulatory proteins, primarily by degrading proteins beyond what are required in the cell. Because proteasomes affect a wide range of regulatory proteins, inhibiting the proteasome can lead to downstream effects that control many cell systems:

The proteins listed on the slide aren’t ones that are well known to many people, but they have effects on the cell cycle of growth and division, can induce programmed cell death (a normal cell function often lost in cancerous cells), and (of course, in keeping with so many novel agents) can have anti-angiogenic properties. In some preclinical (lab-based) research, velcade can enhance the effects of chemotherapy against many cancer cell lines. In several models, adding velcade can overcome resistance to chemotherapy, although this work has been in the lab and not the clinic, and it has focused on different cancer types than lung cancer (bladder, pancreas, prostate, colon...).

Clinically, velcade is given as a very brief (6 second) IV push, and much of the early work gives it twice weekly for two weeks out of three, a pretty inconvenient schedule. More recently, it’s been studied increasingly on a schedule of a higher dose twice weekly for two weeks,
followed by a week off. The most common side effects of velcade have been markedly decreased blood counts and fatigue, which some patients have described as quite profound.

Several clinical trials have been conducted with velcade in lung cancer, and others are ongoing. Dr. Michael Fanucchi led a randomized phase II trial with 155 patients with advanced NSCLC who had previously received one line of prior chemotherapy to receive either velcade alone or the combination of velcade and taxotere (abstract here).

There were several important results from this study. The first point was that velcade has single-agent activity, with a response rate of 8%, which isn’t astounding, but remember that our best agents, and the ones FDA-approved and most commonly used for lung cancer (taxotere, alimta, tarceva) also have a response rate that is essentially identical. But the other arm, receiving the combination of taxotere and velcade, had a response rate of just 9%, the same as what taxotere does on its own. However, the combination did have a much higher stable disease rate, of 45%, compared with 21% for velcade alone. And the combination also had a median time to progression of 4 months, compared with just 1.5 months for the velcade alone:

![Diagram](image)

There have been a few anecdotal reports of impressive results of velcade in some patients with advanced BAC:

![Images](image)

Although not numerous, these results were encouraging enough to lead to dedicated trials of velcade in BAC. A trial run by the manufacturer, Millenium Pharmaceuticals, in which velcade was given twice weekly, was conducted several years ago. The results have not ever been
reported which is usually not a good sign; you don’t keep breakthroughs a secret. Another trial with velcade for BAC is being run by the California and Pittsburgh Cancer Consortium (it’s not just politics that makes strange bedfellows – who would have guessed a cancer research consortium would link several California institutions and the University of Pittsburgh?). In this latter trial, the velcade is being given weekly for two weeks followed by a week off. So velcade will certainly get the chance to show what it can or can’t do for BAC.

Velcade has also been studied in recurrent SCLC (abstract here), where SWOG investigators enthusiastically enrolled 60 patients, hoping for another option for this population. Unfortunately, there was just a single responding patient on the trial, which led SWOG to consider this approach not active enough to pursue further.

Next, we’ll turn to some combinations of velcade with chemo or targeted therapies.