Vorinostat for NSCLC: Not a home-run, but at least swinging for the fences

Substantial resources are spent on large, expensive trials to demonstrate small survival advantages in lung cancer. For example, 889 patients entrusted their care to the phase III SATURN trial of maintenance erlotinib, following treatment with a platinum doublet. At ASCO, we learned that these patients were rewarded with a one week improvement in PFS, and at World Lung, we learned that they lived a month longer. The FDA’s advisory committee recommended against approving erlotinib for maintenance therapy based on this modest benefit.

I am among many oncologists who take a two-faced view on small advances in care. On the one hand, I use advances with modest benefits in my clinic. I do not consider financial cost/benefit when adding avastin to platinum-based doublet therapy for patients with non-SqCC; I even use cetuximab, with more modest benefits, at times. While I use these small advances regularly in my clinic, I take a very different perspective when talking to other investigators, where I argue that we should be swinging for the fences, not trying to get more base-hits. Along the way, we will make minor advances and should use them, but the real goal should be to either cure cancer, or develop non-toxic drugs capable of turning cancer into a chronic disease.

With this perspective in mind, agents that can potentially overcome resistance in lung cancer are of particular interest to me and the histone de-acetylase inhibitors fit this mold. As I am working on a trial of a histone de-acetylase inhibitor for small cell lung cancer, these agents were already on my mind when I read the results of a new study in JCO.

Proteins are the tools of the cell do to all the things that it needs to do — examples of proteins include receptors (here EGFR is probably most famous) and the signal transduction cascade that result from signaling to a receptor. In order to make a protein, the cell starts with the DNA blueprint that is housed in a structure called the nucleus. The nucleus can be thought of us a little fortress-enclosed island containing stacks of blueprints in a big lake that is the cell. The DNA is transcribed into stuff called RNA, which travels out of the nucleus into the cytoplasm (which could be thought of like the water in the lake). In the lake, the RNA attaches to a structure called the ribosome (think of it as a small, floating protein factory) where it is translated into a protein. Most things done by cells, whether normal or cancer, depend on proteins, including the bad things that cancer does and including the death cascades that we’d like to activate within cancer cells. All of the new biologic therapies, such as cetuximab and tarceva seek to modify proteins in some way. For example, cetuximab is an antibody to the EGFR and tarceva is a small-molecule tyrosine-kinase inhibitor (a lot of big words to say that it stops the signaling from the receptor within the cancer cell). Cytotoxic (cell-harming or killing) chemotherapies are the traditional agents. They are all essentially poisons that damage the DNA of rapidly dividing cells. Since cancer cells divide a lot, they are more susceptible to these poisons than normal body cells that, for the most part, shouldn’t be dividing.

Unfortunately, we have witnessed that cytotoxic chemotherapy does not cure lung cancer. How
do cancer cells evade therapy? One potential way is by going to sleep. If a lung cancer cell happens to be taking a snooze while the chemo is passing by, instead of replicating, it could avoid dying from the chemo. Enter histone de-acetylase inhibitors (henceforth HDACi).

DNA exists wrapped around structures called histones. These can be wound tightly, or they can be looser. When looser, the DNA is more active and prone to transcription and when tighter, it is more quiescent. Thus, HDAC inhibitors seek to “wake up” the cancer cells in time to see the chemo. They also influence the action of several players known to be important in cancer, death cascades, and chemotherapy sensitivity—heat shock protein 90, hypoxia-inducing factor alpha, and alpha tubulin. For more information on HDAC inhibitors and the rationale for trying vorinostat in lung cancer, see Dr. West’s 2007 post.

So, it’s a cool science idea. What next? (see slides 14-16 of this link for a review of the progression from idea to improved cancer therapy) Well, it worked well in cell-cultures, so it went to phase I testing, where Dr. West covered the promising results. Since it was safe and had hints of efficacy, it went to phase II testing and the results were just published.

The trial randomized patients with stage IIIB-wet or IV to either carbo/taxol/placebo or carbo/taxol/vorinostat. The primary endpoint was response rate (RR), and the study was positive—RR increased from 12.5% in the placebo arm to 34% with vorinostat (p = .02). This may have been the primary endpoint of the study, but as we’ve talked about many times before on GRACE, this is a surrogate measure—we don’t care about cancer shrinking per se unless it leads to people feeling better and living longer. Did it? Here are the progression free survival and overall survival curves:

![Progression-free survival](image1.png)

![Overall survival](image2.png)
As you can see, there was a trend towards improvement of both progression-free and overall survival. While neither measure met statistical significance, the trial was not powered for these measures. Further, the survival curve does maintain separation as time passes, with even a hint of widening. While not a cure for lung cancer, the magnitude of the potential survival advantage is meaningful, and the regimen is thus worthy of further study. But, what kind of further study is indicated? The authors look at the toxicity data and do something impressive and rare for a positive study: they suggest trying to do better before going to a phase III trial. Instead of replicating the two large tables on toxicity, I’ve made my own summarizing only the toxicities which were worse with vorinostat:

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/vomitting</td>
<td>13</td>
<td>3</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>20</td>
<td>8</td>
<td>0</td>
<td>7</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>0</td>
<td>11</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>—</td>
<td>9</td>
<td>11</td>
<td>—</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

The authors looked at this toxicity and then asked the consequence of it. A look at the table for reasons for treatment discontinuations is revealing:

First, 34% of patients on the placebo arm stopped therapy because it wasn’t working, compared to only 18% on the vorinostat arm—so the therapy does control cancer growth. Second, 24% of patients stopped therapy early on the experimental arm because of toxicity compared to only 9% on the experimental arm. So, not only did vorinostat toxicity cause direct side-effects (likely reducing quality of life), it also caused many patients to stop a regimen that can help delay cancer progression (which in turn improves both duration and quality of life). Instead of slapping high-fives and moving on to phase III testing, the authors did
something courageous—they concluded that alternative schedules combining these drugs should be first tested in the phase II setting to try to get a better regimen with less toxicity. Kudos to them.

Where is vorinostat going in NSCLC? A search of clintrials.gov reveals much of the ongoing work that we can look forward to seeing results from:

- Validation of molecular targets of vorinostat- Patients in this study will receive vorinostat before surgical resection. Their tumors can then be studied to validate biomarkers for vorinostat in lung cancer.
- Multiple trials in combination with erlotinib or gefitinib
- Vorinostat together with paclitaxel and radiation for stage III cancer
- Multiple trials in combination with proteosome inhibitors
- Combination with palliative radiation
- Combination with stereotactic radiosurgery for brain mets

There is also exciting work going on with vorinostat in other cancers (including SCLC) and other HDAC inhibitors are undergoing testing in NSCLC. For now, vorinostat in NSCLC may be headed back to the minor leagues for a season, but it holds the promise of returning as an MVP.