Sorafenib/Nexavar in Non-Small Cell Lung Cancer

Sorafenib, or Nexavar, is an oral “multi-kinase inhibitor”. Kinases are specialized proteins that coordinate communication networks inside the cell and can modulate cancer cell growth as well as angiogenesis, the tumor blood supply. While many of the molecularly targeted agents I have discussed previously have demonstrated activity in lung cancer and sometimes other tumors, I have been discussing agents that primarily target one important cell process or another. Multi-targeted agents can potentially affect multiple relevant signaling cascades at once, but it isn’t clear yet whether they work better than our single-targeted options, or combinations of several single-targeted drugs together. There may also be the possibility of developing new combinations of side effects from one agent that hits multiple targets at once.

Great, but does it work? Fortunately, it does, at least in some tumor types. Sorafenib is currently approved by the US FDA for treatment of advanced kidney cancer, where it was studied in a randomized, placebo (sugar-pill) controlled trial of over 900 previously treated patients. This trial demonstrated that patients treated with nexavar at 400 mg by mouth twice daily went more than twice as long before developing progression of disease compared to the patients who received a placebo. There was also an improvement in overall survival in patients who received nexavar. It was generally well tolerated, with the main side effects being diarrhea, rash, fatigue, a “hand/foot syndrome” of redness and burning on the palms and soles, hair loss, and nausea/vomiting.

It has also been studied in lung cancer, but in a limited capacity thus far. At this year’s ASCO meeting, our annual huge US-based oncology conference, a trial (abstract by Gatzemeier and colleagues here) was presented of 52 previously treated patients (including prior treatment with EGFR inhibitor therapy), without restriction by type of NSCLC (squamous cell carcinoma was permitted), and allowing patients with brain metastases but no symptoms from them. They received nexavar at 400 mg orally twice daily until they developed evidence of progression of disease or prohibitive side effects. While there were no patients who demonstrated enough tumor shrinkage to be considered an objective response, 30 patients (59%) had stable disease for several months, with the “median” progression-free survival in those patients with stable disease going out to 5.5 months. And 2 of the patients had been on treatment for more than two years without progression. Moreover, there were patients who showed some degree of tumor shrinkage even if they didn’t have enough to be considered a “response” by the rigid trial criteria. The figure below is the “waterfall plot” of the patients on treatment (you can see from the appearance of the figure why it’s called that), which shows the total volume of disease measured on CT scans, going from most growth on the left side to most shrinkage on the right side, and the horizontal line in the middle being no change. Bars above the line mean the cancer grew overall, and bars extending below the line are tumor shrinkage. Obviously, the folks with progressive disease (PD), the red bars, are clustered to the left, and the folks with stable disease (SD) are clustered toward the right. But you can see that some patients had a lot of tumor shrinkage but didn’t count as a responder, potentially because their response was not confirmed in another CT scans or some other exact criterion of response on the trial that they didn’t meet. And some patients with SD did have a bit of increased tumor volume.
The main point from the waterfall plot is that there were patients with tumor shrinkage that didn’t meet the criteria for a response, but I would bet that they received meaningful benefit from the treatment.

Side effects were generally mild to moderate, primarily the ones described above of diarrhea, hand-foot syndrome, fatigue, nausea, also elevated blood pressure, itchiness, and dry skin/rash. Importantly, because this agent also has antiangiogenic activity like avastin, bleeding was seen as well, including nosebleeds in 3 patients, but also one death from fatal bleeding from the lung (pulmonary hemorrhage) in a patient with a squamous cancer near the middle of the chest that cavitated (hollowed out during treatment). This actually happened 30 days after stopping the drug, and actually followed radiation treatment to that area. It underscores, however, that while risk of bleeding was not at the same level as was seen with avastin, particularly in the patients with squamous cancers, bleeding risk may be an issue with several drugs that affect the tumor blood supply.

Dr. Joan Schiller (now at University of Texas, Southwestern, in Dallas), who chairs the lung cancer committee for the Eastern Cooperative Oncology Group (ECOG), has also been doing important early work with sorafenib. She presented data that demonstrated safety and encouraging activity in a small study of the combination of sorafenib with the standard chemotherapy doublet of carboplatin and paclitaxel. There is now an international trial being initiated for first-line treatment of advanced NSCLC (all subtypes), to be treated with carboplatin/paclitaxel alone or with sorafenib 400 mg by mouth twice daily:

In addition, ECOG is conducting a trial (E2501) of sorafenib compared with a placebo in patients who have received at least two prior types of chemotherapy for advanced NSCLC. A total of 311 patients are planned to be enrolled over a three year period. Further information about the E2501 trial, including participating sites, is available here.

Because we now live in a world where avastin is a potential standard of care for the patients eligible to receive it for first-line therapy, the lung cancer treatment world may potentially be divided into the group of avastin-eligible patients (see my posts on avastin and ECOG 4599 trial for details) and avastin-ineligible patients. We are starting to see different trials offered for
the two different groups. For instance, the Southwest Oncology Group (SWOG) is developing a trials of chemo (actually cisplatin and taxotere) with sorafenib in first-line treatment of patients with advanced NSCLC who would not be eligible for avastin, including patients with squamous cancers. This trial and others will help clarify whether the bleeding complications seen in a minority of patients who receive avastin, and an apparently particularly higher risk in patients with squamous cancers, are also seen with other antiangiogenic drugs at a frequency that makes this *whole class* of drugs unsafe for certain patients.

Finally, I am opening a trial at my own institution of single-agent sorafenib at 400 mg by mouth twice daily as a later treatment option for patients who have bronchioloalveolar carcinoma, or any never-smoker with a lung adenocarcinoma. This trial, which is still a few weeks away from opening up, will be in a few dozen patients and give us an idea of whether there are particular patient subgroups that may do especially well with sorafenib. If we could identify the few patients who may go years without progressing, and may even show meaningful tumor shrinkage, it would be a great benefit for the lung cancer field.

I'll update as more clinical trials with sorafenib become available.