

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Lessons Learned From the Development of Kinase Inhibitors

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H&O What are some of the main challenges encountered in the development of kinase inhibitors?

CS The challenges have changed over the past 10 years. Initially, the challenge was whether it was chemically possible to isolate inhibitors that would block a specific kinase without causing a lot of nonspecific side effects. The success in using high throughput chemical screening to discover and optimize inhibitors that are relatively specific has been remarkable. Today, if one would like to develop an inhibitor for a kinase, it is almost a given that it can be found. The bigger challenge now is how to use the inhibitors in the right clinical setting. It is difficult to identify in advance which patients are most likely to be dependent upon the kinase that is being targeted with the specific inhibitor (ie, how to match the right kinase inhibitor to the right patients). The solution lies in the discovery of predictive biomarkers, such as HER2 amplification in breast cancer predicting for sensitivity to the HER2 antibody trastuzumab (Herceptin, Genentech).

H&O Resistance has been an issue with kinase inhibitors. What strategies are being considered to overcome this problem?

CS There are a number of kinase inhibitors for which the mechanism of resistance has been unraveled. The most common mechanism with various kinase inhibitors is mutations in the target kinase, which interfere with the ability of the inhibitor to bind the target (but without impairing the activity of the kinase). This theme was seen initially in leukemia and now in lung cancer and sarcoma, with additional examples cropping up in other cancers.

The solution is to develop a second generation inhibitor that will still work against the mutant forms of kinases so that it can be used upfront, or as a second-line drug alone or in combinations. Dasatinib (Sprycel, Bristol-Myers Squibb) and nilotinib (Tasigna, Novartis) are examples of second generation inhibitors of BCR-ABL (following imatinib [Gleevec, Novartis]) that retain activity against many imatinib-resistant mutants of BCR-ABL. There are other cases of resistance where the tumor cell gets around the inhibition of the target kinase A by amplifying another closely-related kinase that can take over the function of the target kinase. This is referred to as a kinase bypass mechanism. One example is amplification of the MET kinase in lung cancer patients with epidermal growth factor receptor (EGFR) mutations who develop resistance to the EGFR inhibitor erlotinib (Tarceva, Genentech/OSI Pharmaceuticals). MET inhibitors are now being evaluated in this setting.

H&O How has the development of second generation kinase inhibitors differed from that of the first generation?

CS The best example is chronic myeloid leukemia (CML) treated with ABL kinase inhibitors. For patients with imatinib-resistant CML, the selection of the second generation inhibitor depends on the knowledge of the mechanism of resistance to the first generation inhibitor. One would need to screen compounds with mutant forms of the target kinase, such as the T315I mutation in BCR-ABL, that cause the resistance in patients who are on current generation compounds, in order to pick the most rational next generation compound. This strategy has worked for CML, and similar strategies are used in sarcomas and lung cancer.

H&O What are some of the technologies that have aided the development of new kinase inhibitors?

CS There are 2 main technologies on the drug discovery end that have aided development. One technology that

is largely used by the pharmaceutical industry is the high throughput, robotic chemical screening of libraries of millions of compounds. Through this process, researchers can quickly identify active compounds. The other technology is the development of panels of different kinases. Once an initial screen of compounds of interest is completed, one can counter screen these compounds against other kinases and pick the ones that are most selective for the kinase of interest. This technology allows screening against hundreds of kinases at a very high speed.

On the clinical development side, the application of genomic profiling technologies, such as DNA sequencing and other methods of assessing the presence or absence of mutations, has allowed patient populations to be more accurately defined for whether or not they are more suited for a specific kinase inhibitor.

H&O Do kinase inhibitors have therapeutic potential in disease states other than cancer?

CS Yes, kinase inhibitors have demonstrated activity in diseases other than cancer. Some interfere with immune system function and therefore would be potentially useful as anti-inflammatory agents or drugs that would prevent graft rejection in transplant recipients. Rapamycin, although not an ATP competitive kinase inhibitor in the classic sense, inhibits the kinase mTOR (mammalian target of rapamycin) and was first approved as an immunosuppressive agent for kidney transplant recipients. However, cancer is still the leading indication for kinase inhibitors. Some kinase inhibitors such as rapamycin that were initially studied in other disease states have been found to also have uses in cancer.

H&O What are some of the agents currently in development?

CS There are hundreds of kinase inhibitor compounds currently in development. Exciting phase I data were presented from a trial of an inhibitor of the kinase BRAF (PLX4032, Plexxicon, Inc) in patients with BRAF mutant melanoma. The study findings resembled the early days of imatinib—the researchers found that patients who responded to the drug had a mutant form of BRAF present in their tumors. Most of the patients enrolled in the study had metastatic melanoma and the maximum tolerated dose is 720 mg twice daily.

There are a number of compounds that target the vascular endothelial growth factor (VEGF) and are being used as antiangiogenic drugs. The initial inhibitors of VEGF such as sorafenib (Nexavar, Bayer) and sunitinib (Sutent, Pfizer) have broad activity; however, several newer drugs currently being studied are more selective agents.

H&O What are the lessons learned from the development of kinase inhibitors since the approval of imatinib?

CS There are a couple of early lessons from the development of kinase inhibitors. The first is that the concerns of toxicity from inhibiting kinases were vastly overestimated; in general, most compounds are extremely well tolerated relative to chemotherapy. The second lesson, which is more of a biomarker issue, is the importance of genetic alteration of the kinase—or of other key proteins in the pathway in which the kinase functions—as being predictive of whether or not the tumor is dependent upon a kinase. Hence, incorporating genomics into early clinical trials evaluating kinase inhibitors is a key lesson in moving forward.

H&O What do you think are the future directions for kinase inhibitors?

CS Ongoing cancer genome projects such as the Cancer Genome Atlas (TCGA) have the goal of identifying all the gene mutations in cancer patients. These projects will generate more examples of kinases that are mutated, and hence those tumors have a high probability of responding to treatment with the right kinase inhibitor. It is unlikely that large populations of patients that we currently do not know about will be discovered; however, small groups of patients who have new mutations may be found. Future research will also analyze kinase inhibitors in combinations—inhibition of 2 or 3 kinases at the same time with the notion that inhibiting only 1 might have a slight effect, but inhibiting 2 or 3 simultaneously will have profound effects on tumor survival. The big challenge in creating novel combination therapies is bringing together the science, economics, and business (ie, companies working in collaboration) sectors.

Also of importance is providing clinical investigators with training in cancer genomics in order to classify patients and mix and match them with specific kinase inhibitors. Just 10 years ago, the cultures of genomics and clinical trials research were completely separate, but now there is growing overlap. We need more young oncologists who can speak the language of both worlds to advance research in personalized medicine.

Suggested Reading

Flaherty K, Puzanov I, Sosman J, et al. Phase I study of PLX4032: Proof of concept for V600E BRAF mutation as a therapeutic target in human cancer. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2009;27(15s):abstr 9000.

The Cancer Genome Atlas. National Cancer Institute. Available at <http://cancergenome.nih.gov/>