Editorial

Is Another Bcr-Abl Inhibitor Needed for Chronic Myelogenous Leukemia?

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The recent success of STI-571 (Imatinib mesylate; Gleevec) in the chronic phase of CML is a milestone in the history of medicine. For the first time, a treatment directed at the molecular basis for a tumor’s occurrence and progression has emerged. Such molecularly targeted agents are the focus of current developmental research, with hopes for applications across a broad range of potential targets and tumors. Huron et al. in this issue of Clinical Cancer Research (1) report the pyridopyrimidine PD166326, representative of a new chemical class, to possess picomolar potency against p210bcrlabl kinase in biochemical assays and nanomolar potency against p210bcrlabl-driven cell lines, both assayed in vitro, but more potent than STI-571 with respect to these endpoints. Given the success of STI-571, however, it is reasonable to question whether there is need and practical value in further pursuing the development of this compound, especially given the limited number of patients (thankfully) afflicted with CML.

The immediate and unflinching answer to this question is a resounding YES! Multiple reasons support this position. STI-571 is an ATP-binding site directed inhibitor with selective activity against the abl, kit, and platelet-derived growth factor receptor kinases. Accordingly, it has shown gratifying activity not only in chronic phase CML but also in kit-driven gastrointestinal stromal tumors and shows promise in platelet-derived growth factor receptor-driven proliferations such as dermatofibrosarcoma protuberas (2–5). However, it is not by any means a perfect drug. Patients with blast phase CML show more limited or essentially no response to STI-571 (6). Multiple mechanisms of resistance are emerging to STI-571, including p210bcrlabl gene amplification (7), mutations (8), and host-related elaboration of α1-acid glycoprotein (9). Thus, one can hardly maintain that the book should be closed on developing bcr-abl-directed therapies.

Another issue arises when one considers the molecular details of how STI-571 and the pyridopyrimidines actually work. Crystallographic studies have documented that both a derivative of STI-571, and STI-571 itself binds to a nonphosphorylated, inactive conformation of the abl kinase (10, 11). Indeed, it is much less active against the fully activated phosphorylated kinase. In contrast, structural studies with a sibling compound to PD166326 demonstrate that pyridopyrimidines can likely bind to both the inactive and active abl conformations. Although analogous co-crystallization studies have yet to be reported with PD166326, this important distinction may connote the ability to more thoroughly suppress kinase activity or at the very least cause a distinct set of resistance strategies to be developed by the tumor in comparison to those used by STI-571. Indeed, Huron et al. (1) demonstrate that certain STI-resistant variants of p210bcrlabl are completely or partially sensitive to PD166326. One might therefore imagine not only the value of pyridopyrimidines in STI-571-resistant patients, but perhaps in combination with STI-571 in CML, hopefully forcing p210bcrlabl to come up with a more sophisticated basis for resistance and therefore increasing the period of benefit from the combined kinase-inhibitor therapy. Ideally, mutant p210bcrlabl to both drugs would function as such a poor kinase that the pace of the disease might be intrinsically altered. This idea is similar to successful strategies to treat mycobacterial and HIV infections.

An additional quite tantalizing feature relates to the spectrum of kinase susceptibilities of PD166326 and its sibs, which differ markedly from that of STI-571. PD166326 has considerable activity against src and src-related kinases such as lck in contrast to STI-571. This has potentially important practical value because src family members hck and lyn are downstream of p210bcrlabl and may be important in mediating the growth-promoting effects of p210bcrlabl. Thus, PD166326 and related molecules may offer multiple points of attack on the growth-promoting pathway used in CML.

For these reasons, however, the pyridopyrimidines as a class have been regarded by some as less attractive than STI-571 because of their potential capacity to affect a larger variety of kinase targets. This leads to an issue that is a matter of intense debate among developers of such drugs. One conventional wisdom is that ultra-selective inhibitors of particular kinases should be pursued to the exclusion of inhibitors that address multiple targets. Yet, as has been observed elsewhere (12), neoplasms commonly use many signaling strategies to deregulate normal growth control mechanisms. What one really would desire are inhibitors with the proper balance of inhibitory capacities or combinations of signal transduction inhibitors with the appropriate mix of activities. No selectivity will likely lose therapeutic index; excessive selectivity may produce a less useful drug. This is philosophically no different from what has emerged in, for example, catecholamine receptor-directed pharmacology: a number (but admittedly not all) really useful drugs have a spectrum of activity across the many different adrenergic receptor subtypes (13). CML, particularly STI-resistant CML, may be the stalking horse that allows expedient demonstration of safety and efficacy of an appropriately chosen pyridopyrimidine and, once available, allow its expedient examination in diseases with a different but susceptible set of kinases from those used by CML.

Other potential strategies to deal with resistant CML exist. Adaphostin (NSC 680410) is a tyrphostin-derived tyrosine kinase inhibitor that affects multiple kinase substrates and therefore is not p210bcrlabl specific. However, it can cause apparent down-regulation of p210bcrlabl expression and is apparently less reversible than STI-571 (14). Heat shock protein 90-directed benzoxquinoid ansamycins such as 17-allylamino, 17-demethoxygeldanamycin (NSC...
330507; 17AAG) likewise cause degradation of p210<sub>bcr/abl</sub> and good inhibition of both wild-type (15) and STI-571-resistant (16) CML cell types or kinases. Although one might argue that these therapeutic opportunities are less purely p210<sub>bcr/abl</sub>directed than one might desire, the pragmatic reality is that both patients and treating physicians care much more about what really works. Therefore, these compounds should also be pursued, at least to the point of initial clinical experiences.

What are the downside issues of PD166326 and other pyridopyrimidines? At the present, there is noteworthy paucity of information regarding their pharmaceutical properties. We have no data indicating the <em>in vitro</em> efficacy in animal models, how they might be formulated, of what pharmacology they demonstrate when administered by various routes, and their safety and toxicity profile. These issues are particularly important; for whatever features STI-571 may lack, it is a very good drug in the sense that <em>in vivo</em> activity closely tracks its capacity to alter p210<sub>bcr/abl</sub> phosphorylation, and human pharmacology closely mirrors that active in mouse models (17). It is wise to remember also that <em>in vitro</em> potency does not always a drug make, and additional research is needed to define the pharmaceutical tractability of the pyridopyrimidines. With sufficient supply of compound(s), all of these concerns could be clarified or lead to defining a good pyridopyrimidine in pharmaceutical terms while preserving their important cellular biological features.

An additional concern is potential corporate indifference. The pyridopyrimidines emerged from an extensive effort from a major pharmaceutical firm to define novel chemotypes with selective activity against various kinase targets (18). The prospect of entering the CML arena, with an established competitor agent, and rather limited market share might understandably cause uncertainty in corporate boardrooms, if not in the trenches of the laboratory scientists. One hopes that the current situation with the pyridopyrimidines can be seen as the opportunity for partnering of private corporate, academic, and government resources that it represents. The science presented in the work by Huron<em> et al. </em>(1) is compelling: this agent and those like it need to be expeditiously advanced to the clinic, assuming good pharmaceutical behavior, or features that allow good pharmaceutical behavior built into subsequent generations of molecules. Whether advanced by the parent company, licensed to more focused, perhaps smaller companies, or studied through new avenues of cooperation among academia, the industry, and government to leverage risks in evaluating niche drugs for the clinic, development of pyridopyrimidines is a matter to consider with urgency.

References


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