STI571: A Sea Change in Cancer Therapeutics or a One Time Event?

By Brian J. Druker, MD

The introduction of STI571 (Gleevec), an agent targeted against the causative molecular event in chronic myelogenous leukemia (CML) has been heralded as a major advance in the treatment of cancer.[1,2] Certainly, the clinical trials with STI571 have validated the concept that a precise understanding of the pathogenesis of a cancer can lead to more effective and less toxic therapies. However, the major question is whether this paradigm can be applied to all cancers, particularly the more common types.

In an era where the words "molecularly targeted therapy" are used frequently, it is perhaps best to define these terms. Cancer cells require the activation of many pathways, including those regulating growth, survival, and angiogenesis. Most current cancer therapies, such as chemotherapy and radiation, attempt to inhibit cellular growth or induce apoptosis. As we learn more about the regulation of cellular growth, survival, and angiogenic pathways, more drugs targeting these pathways will emerge. These agents potentially would be useful for the treatment of many different types of tumors, but their specificity for the tumor may be a limiting feature. Examples of these agents include cell cycle inhibitors, apoptosis promoting agents, telomerase inhibitors, and antiangiogenic agents. As agents are developed that target specific genes or proteins in these pathways, I would refer to them as molecularly targeted agents.

However, I would distinguish these agents from agents that target specific pathogenetic events in a tumor. Each tumor is likely to have a unique set of abnormalities that are the critical initiating events in their natural history. Drugs that target these abnormalities would likely have narrow spectra of activity and would be referred to as molecular pathogenetically targeted. Examples of these agents include STI571 targeting Bcr-Abl in CML and *c-kit* in gastrointestinal stromal tumors (GIST), all-trans retinoic acid targeting PML-RARa in APL, and trastuzumab (Herceptin) targeting Her-2/neu in breast cancer. Obviously, targets in the general category may overlap with targets in the molecular pathogenetic category. For example, cyclin D1 or bcl2 overexpression in subcategories of lymphoma would fit both specific and general categories. In the case of an agent that targets a molecular pathogenetic target, the presence of the target wouldn't necessarily equate with pathogenesis. Rather, an indication of aberrant activity or expression would be a prerequisite for using an agent that targets these abnormalities. As an example of this concept, the response rate to STI571 is significantly higher in patients with mutated/activated *c-kit* in the GIST studies as opposed to patients who express the wild-type *c-kit*.[3] In addition, the minimal myelosuppression seen in the GIST studies, despite expression of *c-kit* on hematopoietic stem cells, suggests that *c-kit* expression is dispensable for normal cellular function. Thus, expression does not necessarily equate with pathogenesis.

In the near future, it is probable that we will see combinations of agents in each of these two categories. Some of the general antitumor agents, such as cell cycle inhibitors, will likely have significant toxicity against normal cells, while the toxicities of other agents in this category are less predictable. Although drugs that target molecular pathogenetic abnormalities might be predicted to have fewer side effects, this will depend on the function of the normal cellular counterpart of the mutated or overexpressed protein. In all cases, resistance to single agents would seem likely, and combinations of treatments with nonoverlapping toxicities will likely remain cancer therapy mainstays. For example, combining trastuzumab with chemotherapy is more effective than either treatment alone.[4]

Another important feature of the clinical trials of STI571 in CML is that as with most malignancies, treatment earlier in the course of the disease yields better results. Specifically, the response rate and durability of responses has been greater in chronic phase patients as opposed to blast phase patients.[5,6] Thus, for maximal utility as a single agent, the identification of crucial, early events in malignant progression is the first step in reproducing the success with STI571 in other malignancies. An equally as important issue is the selection of patients for clinical trials based on the presence of an appropriate target. Again, in the CML experience, patients with activation of Bcr-Abl were easily identifiable by the presence of the Philadelphia chromosome. When all of these elements are put together, a critical pathogenetic target that is easily identifiable early in the course of the disease, remarkable results with an agent that

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targets this abnormality can be achieved. The obvious goal is to identify the early pathogenetic events in each malignancy, to develop agents that specifically target these abnormalities, and to develop techniques that allow the reliable detection of cancers at an early stage, presumably when they have fewer genetic changes as compared to normal cells.

In an era where expression profiling of cancers has become commonplace, one of the challenges will be to develop assays to validate a target as a pathogenetic target. Presumably, hundreds of genes will be up- or down-regulated in a cancer and it will be necessary to determine which of these genes are critical to the pathogenesis of the cancer. Another issue will be the number of pathogenetic events in an early malignancy. For example, will ductal carcinoma in situ be due to a handful of genetic changes or will there be hundreds? Both of these issues impact directly on the economics of drug development as discussed in this issue of *Oncology Spectrums*. If early breast cancer is split into a hundred different diseases, would these targets be attractive to a large pharmaceutical company? One of the features of this problem that is already changing is the approach to drug development, also discussed in this issue. Fueled by advances in structural biology and computational chemistry leading to structurally directed medicinal chemistry, the speed of preclinical drug development has accelerated greatly. The next step will be for clinical trials to keep pace as more and more molecularly targeted agents become available. This will also require an evolution in our thinking about clinical trials as discussed in the article about STI571 in this issue.

When you put together our current abilities to profile cancers, the advancements in drug development, and a dissection of the elements leading to success of STI571, I am optimistic that we are witnessing a change in the way that oncology will be practiced. Given the complexities of most cancers, there is still much work to be done, but I firmly believe that we are on the right track. OS

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