The Advent of Targeted Therapeutics and Implications for Pathologists

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Gleevec (STI571, imatinib mesylate) is the first major success in the development of targeted anticancer therapies. This oral drug was designed “from the ground up” as an inhibitor of the ABL tyrosine kinase, which becomes constitutively expressed and activated as a result of its fusion to BCR in chronic myelogenous leukemia (CML). Early clinical studies were so promising that the US Food and Drug Administration approved the drug in record time in May 2001. The article by Hasserjian et al1 in this issue of the Journal suggests that much remains to be learned about the mechanism of action of Gleevec. In this study, the authors found that Gleevec actually induces myeloid differentiation without eliminating the Philadelphia chromosome–positive clone. Previously it was thought that the primary mechanism of action of Gleevec was to slow growth and induce apoptosis of CML cells. It now seems that part of the beneficial effect may actually be mediated through this differentiation mechanism.

The story of Gleevec development is an interesting one, illustrating the complexities of the drug development process and how researchers in academics and industry work together to bring a new drug to the marketplace.2,3 The pioneering work of Peter Nowell, MD, and David Hungerford, MD, in 1960 conducted at the University of Pennsylvania led to the recognition of the Philadelphia chromosome in CML. This laid the groundwork for later pivotal work by Janet Rowley, MD, and David Baltimore, PhD, among many others, that led to the recognition of the BCR-ABL fusion gene and, ultimately, to the role of its protein product as a constitutively active tyrosine kinase. The early development of tyrosine kinase inhibitors of BCR-ABL was carried out by a team at Ciba-Geigy (later acquired by Novartis, Basel, Switzerland), but it is likely that STI571, the drug ultimately known as Gleevec, would not have made it to clinic without the persistent efforts of Brian Druker, MD, an oncologist at the University of Oregon, Portland. The Gleevec story is far from over, as many patients with CML treated with Gleevec still experience relapse within 1 year, and some significant side effects, such as nausea, cramps, diarrhea, and hepatotoxic effects, have been encountered.4 Nevertheless, the success of Gleevec strongly validates the power of targeted therapies for cancer.

Gleevec is, of course, only the tip of the iceberg. As the sampling in Table 1 shows, many more drugs are being tested in clinical trials, and hundreds more types of targeted therapeutics are in late preclinical or early clinical development. More than 100 new therapies are being tested in clinical trials for hematologic malignant neoplasms alone.5 What will be the effect of this wave of targeted therapeutics on pathologists? Certainly pathologists will provide support for clinical trials, in which they are likely to see pathology they have not seen before. Some past examples of this include the myeloid hyperplasia that accompanies granulocyte colony-stimulating factor therapy and the induction of myeloid differentiation of acute promyelocytic leukemia by all-trans-retinoic acid or more recently by arsenic trioxide therapy. In research such as the study by Hasserjian et al,1 increasing numbers of academic pathologists will focus attention on the pathologic responses to new therapies. As more experimental drugs come into clinical use, it is highly probable that adverse side effects may be first recognized by pathologists. In addition, it is likely that pathologists will have a major role in harvesting and analyzing tissues in therapeutic failures, determining, for example, whether mutations have occurred in the molecular target or, ultimately, even more global questions of other genes that may explain why
disease in some patients responds and disease in others does not. For example, patients experiencing relapse after Gleevec therapy show point mutations in ABL that seem to confer resistance to the drug.6

In addition to making the histopathologic diagnoses, pathologists will face a greater demand for determining whether a specific molecular target is present before therapy. A typical example of this is determining the estrogen receptor and progesterone receptor status and HER-2 status of patients with breast cancer. Another simple example is verifying expression of CD20 in non-Hodgkin lymphomas in preparation for rituximab therapy. It will be a challenge to decide what technology to invest in to economically provide increasingly sophisticated testing. What if pathologists are expected to provide analysis of point mutations, for example, for FLT3 mutations in acute myelogenous leukemia? What if the number of relevant genes to be tested for mutations number in the tens or hundreds? If the use of targeted therapeutics personalized for each patient becomes reality, it seems likely that molecular diagnostic testing will become more and more consolidated and possibly dominated by a small number of commercial or major academic center laboratories.7

The targeted therapeutic revolution also will provide some attractive alternative career paths for residents currently in training. Increasing numbers of pathologists will be needed to assist with discovery and preclinical development of targeted therapeutics in academics and industry. Academic institutions are likely to develop increasingly close ties with industry as more and more tissue is required to support development of targeted therapeutics, and this will continue to pose challenges as institutions strive to make arrangements that are ethical, compliant with government regulations, and equitable in terms of intellectual property. Along these lines, we can expect that staff pathologists will spend increasing time banking tissues, verifying diagnoses of tissues, constructing tissue arrays, and using techniques such as laser capture microdissection to isolate tissue for high-throughput analysis such as microarray and mass spectroscopy.

These are indeed exciting times for pathologists. It will be important for us, and more important for the residents we are training, to develop the skills required in areas such as information technology and molecular diagnostics, to develop an understanding of the workings of institutional review boards and government regulatory agencies, and to meet the challenges and take advantage of the opportunities in this new era.

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References


