EDITORIALS

Overcoming Resistance to Targeted Anticancer Drugs

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More than a decade ago, imatinib, an agent that has a specific inhibitory interaction with the BCR-ABL fusion protein, was introduced for the treatment of chronic myeloid leukemia (CML). The introduction of this agent dramatically changed researchers' understanding not only of the role of tyrosine kinases as targets for oncology drugs (despite the conserved status of protein kinase domains in nature), but also their ability to conceptualize and test novel molecular mechanisms of action and drug resistance in solid tumors such as adenocarcinoma of the lung as well as in hematopoietic cancers.[1,2] The underlying genetic instability of most cancers favors the phenotypic expression of complex resistance patterns during the selective pressure imposed by drugs designed to impair the proliferative potential of tumor cells.[3] For most of the history of treatment of systemic cancers, attempts to understand resistance to cancer chemotherapy focused on mechanisms thought to be specific to one drug class or another.[4] However, recent studies with the use of more sophisticated techniques have, not unexpectedly, also revealed pleiotropic resistance patterns associated with the majority of nonspecific cytotoxic agents; these patterns include alterations in drug transport, tumor-cell apoptosis, the DNA damage response, the tumor microenvironment, and the function of cancer stem cells.[5]

Resistance to therapy for systemic cancer either is apparent soon after the initiation of treatment (primary resistance) or develops after an initial therapeutic response (acquired resistance). Primary drug resistance to both cytotoxic chemotherapy and molecularly targeted therapeutic agents remains a largely unsolved problem in oncology because of the extraordinarily broad range of potential resistance mechanisms involved.[5] The current approach to acquired resistance has changed markedly since the first generation of targeted cancer therapies (imatinib for CML, trastuzumab for breast cancer, and erlotinib for lung cancer) became part of routine clinical practice over the past 15 years.[6,7] These agents were developed to interfere with a specific, limited molecular landscape such as cell-surface receptors, ATP-binding pockets, and enzyme active sites, often of known structure and conformation. Thus, it is now possible to determine by means of molecular sequencing of DNA from tumor biopsy specimens (or circulating tumor cells or DNA) whether genetic or epigenetic alterations have developed at the time when clinical evidence of drug resistance becomes manifest. These efforts, when used together with sensitive, RNA-based or protein-based techniques, can suggest specific pathways of drug resistance and potential alterations in treatment strategies that may be useful for individual patients.[8] The rapid delineation of molecular mechanisms of clinical drug resistance at the structural level, which is difficult if not impossible for broad-spectrum cytotoxic molecules, together with modern tools of chemical biology and in vitro toxicologic screening, may permit drug development to occur on an accelerated schedule for well-characterized biologic targets.

In this issue of the *Journal*, Cortes et al.[9] provide a striking example of the fruits of current approaches to cancer-drug development. On the basis of the results of their multicenter, phase 2 clinical trial, ponatinib, a third-generation inhibitor of both the unmutated and mutated BCR-ABL fusion product, was granted accelerated approval in 2012 by the Food and Drug Admin-

istration (FDA) for treatment of patients with CML or Philadelphia chromosome–positive acute lymphoblastic leukemia that was resistant to prior tyrosine kinase inhibitor therapy or in whom there were unacceptable toxic effects from these agents. Less than 5 years was required to bring second-generation tyrosine kinase inhibitors from concept to FDA approval for imatinib-resistant CML. An even shorter gestation was possible for ponatinib, which was synthesized to avoid resistance produced by the threonine-to-isoleucine mutation at position 315 (T315I) of the ABL kinase domain — a mutation commonly observed in patients who no longer had a response to imatinib or to the other tyrosine kinase inhibitors approved for the treatment of CML (dasatinib or nilotinib).

More than half the patients with tyrosine kinase inhibitor–resistant chronic-phase CML had a durable (>12 months) cytogenetic response, irrespective of their T315I mutation status. The high level of clinical benefit observed in patients with and without known resistance mutations who received ponatinib was associated, however, with a surprisingly high frequency of arterial thrombosis and other severe vascular adverse events. Because serious toxicities have been confirmed in subsequent trials of ponatinib, considerable care must be exercised in weighing the potential risks of cardiovascular toxic effects versus the benefits of ponatinib treatment in patients without a broad range of other therapeutic options.[10] Much remains to be learned about both the mechanism of action and the toxicity of this agent.

It seems clear, in addition, that this practice-changing trial of ponatinib will have a major impact on the future of cancer-drug discovery. The study adds prominently to a growing literature that provides support for the routine molecular characterization of tissue samples from both hematopoietic cancers and solid tumors at baseline and during therapy to optimize the choice of treatment. It also provides support for a new drug-discovery paradigm leading from rapid ascertainment of new resistance mechanisms to targeted agents to equally rapid creation of molecules to address these mechanisms and rapid advancement of such compounds into clinical use. Finally, it can be expected that a continuing examination of the molecular features of cancers that acquire resistance to ponatinib will lead to new insights into the biology of CML.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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The Role of the Intrarenal Resistive Index in Kidney Transplantation

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The evaluation of renal allografts has progressed little over the past 20 years. The serum creatinine level and glomerular filtration rate (GFR) remain the basis of renal-allograft assessment; other methods, such as protocol-driven biopsies and molecular profiling, are not yet widely used.