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Drug Offers New Options for Leukemia Patients

Dasatinib, an experimental drug under development by Bristol-Myers Squibb, reverses the signs and symptoms of patients whose chronic myeloid leukemia has failed to respond to Gleevec, which is considered the standard of treatment for the disorder.

In a study published in the June 15, 2006, issue of the *New England Journal of Medicine (NEJM)*, Howard Hughes Medical Institute (HHMI) researchers at the University of California, Los Angeles, and colleagues at M.D. Anderson Cancer Center and Bristol-Myers Squibb in Princeton, NJ, report data from phase I human clinical trials of the compound, dasatinib (BMS-354825). Phase I clinical trials evaluate drug safety and toxicity at different dose levels in a small number of volunteers.

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The studies published in *NEJM* indicate that dasatinib can be used to overcome Gleevec resistance in patients who have chronic myeloid leukemia (CML). Patients enrolled in the study had experienced a worsening of the disease or intolerance when treated with Gleevec.

Study leader, HHMI investigator Charles L. Sawyers, and colleagues at UCLA's Jonsson Comprehensive Cancer Center, report that dasatinib successfully circumvented Gleevec (imatinib) resistance in 68 of 84 patients treated with the drug during phase I clinical trials at UCLA and M.D. Anderson Cancer Center. Resistance to Gleevec develops when patients acquire mutations in an enzyme that is targeted by Gleevec.

(The studies) provide immediate hope for patients in whom CML cells have developed resistance to imatinib, wrote HHMI investigator Brian J. Druker of Oregon Health and Science University in an accompanying editorial in *NEJM*. They show that the pace of new drug development can be impressively rapid.

In early June 2006, the Food and Drug Administration's Oncologic Drugs Advisory Committee voted to recommend accelerated approval of dasatinib for the treatment of adults in all phases of CML with resistance or intolerance to prior therapy. The committee based its recommendation on review of data that included safety and efficacy results from five international, multi-center Phase II trials, together with other supportive data. Similar to the Phase I study, Phase II trials analyzed data from all phases of CML in patients resistant or intolerant to prior therapy and will be fully reported in later publications.

Speaking about the *NEJM* study, Sawyers said, Our study examined patients in all phases of CML, including the chronic phase, the accelerated phase, and blast crisis. The patients responded quite well to this drug, and we observed no serious side effects. Their responses to the drug are durable, and the drug works in advanced stages of the disease, including blast crisis.

Of the 84 patients enrolled in the study, 40 had chronic-phase CML; 11 had accelerated-phase CML; 23 had myeloid blast crisis; and 10 had lymphoid blast crisis. Drug dosages were fine-tuned for each patient based on detailed studies that examined how well the drug inhibited its target - a technique that was pioneered by Sawyers's group for use in earlier studies in mice. Another novel facet of the study, Sawyers said, is that each patient's resistance-enhancing mutation was sequenced by Bristol-Myers Squibb scientists. This provided a wealth of information about the type of mutation carried by each patient, and allowed the researchers to correlate how the drug responded to each type of mutation.

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The identification of dasatinib as a lead compound was a direct result of researchers' learning the molecular explanation for why patients develop resistance to Gleevec. Sawyers noted that just as Gleevec was developed as a molecularly targeted inhibitor, the next generations of kinase inhibitors, which include dasatinib, are being refined and improved by structural biology studies that show how the drugs fit with their target, and how mutations alter the shape of that target.

In this case, the target of both Gleevec and dasatinib is the Abelson tyrosine kinase (ABL), an enzyme that becomes overactivated by a chromosomal mix-up that occurs during blood cell development. The genes ABL and BCR, which are located on different chromosomes, become fused and express a hybrid BCR-ABL enzyme that is always active. The hyperactive BCR-ABL, in turn, drives the overproliferation of white blood cells that is the hallmark of CML. Dasatinib differs from Gleevec in that it is a sloppier inhibitor that does not hold its target to such tight structural constraints.

There are currently about 50 known Gleevec-resistance mutations, each of which hampers Gleevec's ability to bind to its target, the ABL kinase. In the case of both Gleevec and dasatinib, there appears to be one particular mutation, known as T315I, which does not respond to either therapy. That

mutation will likely require a different drug, and researchers are working on that now, said Sawyers.

Sawyers, who in addition to being a researcher, also sees cancer patients at UCLA, has long been hunting for an explanation of Gleevec resistance. The development of dasatinib is deeply rooted in scientific literature spanning several different fields, including molecular oncology and structural biology.

This is the first drug to get around kinase resistance, and that has broad implications for CML and other cancers, Sawyers said. One could envision using dasatinib in a combination kinase inhibitor therapy for CML.