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WHAT'S HOT IN... MEDICINE , September/October 2008

In Two Different Cancers, Success with Drugs New and Old

by David W. Sharp



No fewer than five papers in the current Top Ten relate to malignant disease, so let us focus for the moment on just two of the newcomers. Papers #8 and #9 are very different, and not just because of the different diagnoses.

The treatment options for patients with chronic myeloid leukemia (CML) have been revolutionized by the arrival of the drug imatinib. This illness is caused by a chromosomal abnormality that results in an abnormally active form of the enzyme tyrosine kinase, and imatinib is an inhibitor specifically aimed at this target. As with any drug, imatinib is not always tolerated. Also, despite the impressive clinical improvements achieved by patients taking this drug, a few leukemia cells stay behind and are prone to further mutation in the relevant gene (known as *BCR-ABL*) so that relapses are possible. In a commentary on paper #8, Dr. Brian J. Druker (*New Engl. J. Med.*, 354[24]: 2594-6, 2006; see also his interview in *Science Watch*, March/April 2003) wonders why pharmaceutical companies would want to plow research-and-development funding into what might ordinarily be thought of as a small market, for CML is "a disease that affects fewer than 5000 patients per year in the United States." One reason, he argues, is that drugs that arrive via genomic or molecular medicine (i.e., drugs engineered to go for specific targets identified via detailed basic research at a subcellular level) can be tested on patients most likely to benefit, so that drug development times might be shortened. Imatinib and the related agent

Medicine Top Ten Papers

Rank	Papers	Cites Mar- Apr 08	Rank Jan- Feb 08
1	S.E. Nissen, K. Wolski, "Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes," <i>New Engl. J. Med.</i> , 356(24): 2457-71, 14 June 2007. [Cleveland Clinic, OH] *178DR	78	2
2	R. Sladek, <i>et al.</i> , "A genome-wide association study identifies novel risk loci for type 2 diabetes," <i>Nature</i> , 445(7130): 881-5, 22 February 2007. [14 institutions worldwide] *138CR	52	†
3	B. Escudier, <i>et al.</i> , "Sorafenib in advanced clear-cell renal-cell carcinoma," <i>New Engl. J. Med.</i> , 356(2): 125-34, 11 January 2007. [15 institutions worldwide] *124NE	59	4
4	R.J. Motzer, <i>et al.</i> , "Sunitinib versus interferon alfa in metastatic renal-cell carcinoma," <i>New Engl. J. Med.</i> , 356(2): 115-24, 11 January 2007. [10 institutions worldwide] *124NE	56	5
5	L.J. Scott, <i>et al.</i> , "A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants," <i>Science</i> , 316(5829): 1341-5, 1 June 2007. [12 U.S. and Finland institutions] *173PS	50	†

dasatinib that is the focus of #8 (and also nilotinib, the subject of a companion paper to #8 [see H. Kantarjian, *et al.*, *New Engl. J. Med.*, 354 (24): 2542-51, 2006; 31 cites this period]) are early successful examples of the new approach to pharmaceutical research that has been nicely described for the more general reader by, for example, Dr. Allen D. Roses (*Lancet*, 355[9212]: 1358-61, 2000).

As reported in #8, the patients with CML (a small number had a specific type of acute leukemia) were resistant to or intolerant of imatinib. A complete hematologic response was achieved in all but 3 of the 40 patients who were in chronic-phase CML, and at a median follow-up of 12 months this response had been maintained in 95%. Major responses were seen in the 31 of the other 44 leukemia patients. This phase I trial included studies of *BCR-ABL* mutations. One mutation (T3151) remains a problem because this genotype does not respond to either dasatinib or nilotinib. Newer agents in the pipeline may resolve this difficulty in time.

If #8 helps with treatment choices in CML, #9 certainly does so for gastric cancer, a much more common disease. In an accompanying editorial, Dr. John S. Macdonald (*New Engl. J. Med.*, 355 [1]:76-77, 2006) sees this "well designed and well executed" phase III trial as one providing "solid evidence that perioperative therapy with a regimen of ECF [epirubicin, cisplatin, and fluorouracil] improves the outcome for patients with respectable gastric cancer identified before gastrectomy." Imatinib, dasatinib, and nilotinib are relatively new drugs. The ECF combination is not, having been devised two decades ago, long before genomic medicine took off. And one of the problems that clinicians and their patients face with stomach cancer is an old one, too. Surgical techniques pioneered in Japan have not been successfully translated into western medicine. This trial, an international one but supported by the U.K.'s Medical Research Council, looked at the effects of giving ECF before and after surgery (perioperative). The results are impressive. For example, the 5-year survival rate was 36% in the group given perioperative ECF compared with 23% in the surgery-only group. In this trial the first patient was randomized in July, 1994, and both the paper and the attendant editorial note that newer drugs are now available (e.g., capecitabine and oxaliplatin). For both chronic myeloid leukemia and gastric cancer there is more to be done. ■

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Keywords: chronic myeloid leukemia, CML, imatinib, imatinib-resistant, dasatinib, Brian J. Druker, gastric cancer, ECF, epirubicin, cisplatin, fluorouracil, stomach cancer..



6	G.J. Moran, <i>et al.</i> , "Methicillin-resistant <i>S. Aureus</i> infections among patients in the emergency department," <i>New Engl. J. Med.</i> , 355(7): 666-74, 17 August 2006. [U. Calif., Los Angeles; Ctrs. Disease Control & Prevent., Atlanta, GA] *074AN	48	8
7	E. Zeggini, <i>et al.</i> , "Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes," <i>Science</i> , 316(5829): 1336-41, 1 June 2007. [10 U.K. institutions] *173PS	45	†
8	M. Talpaz, <i>et al.</i> , "Dasatinib in imatinib-resistant Philadelphia chromosome-positive leukemias," <i>New Engl. J. Med.</i> , 354(24): 2531-41, 15 June 2006. [M.D. Anderson Cancer Ctr., Houston, TX; U. Calif., Los Angeles; Bristol-Myers Squibb, Wallingford, CT; Howard Hughes Med. Inst., Chevy Chase, MD] *052KU	43	†
9	D. Cunningham, <i>et al.</i> , "Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer," <i>New Engl. J. Med.</i> , 355 (1): 11-20, 6 July 2006. [9 U.K. and Netherlands institutions] *060DT	39	†
10	C.E. Geyer, <i>et al.</i> , "Lapatinib plus capecitabine for HER-2 positive advanced breast cancer," <i>New Engl. J. Med.</i> , 355 (26): 2733-43, 28 December 2006. [15 institutions worldwide] *120UA	38	†

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