WHAT'S HOT IN... MEDICINE , November/December 2009

Personalized Therapy Arrives for Patients with Colorectal Cancer

by David W. Sharp

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Earlier this year the American Society of Clinical Oncology (ASCO) offered as a "provisional clinical opinion" the statement that "all patients with metastatic colon cancer should have their tumors tested for *KRAS* mutations" (*J. Clin. Oncol.*, 27[12]: 2091-6, 2009). Others have said much the same thing—for example, it should be "standard practice" to restrict colon-cancer treatment targeted at the epidermal growth factor receptor (EGFR) to patients whose tumors test positive for wild-type (non-mutated) *KRAS* (D. Z. Chang, *et al.*, *J. Hematol. Oncol.*, 2:18, 2009).

The National Comprehensive Cancer Network clinical guideline on colon cancer reflects this change, too; in the U.K. the documentation for a clinical trial of chemotherapy with or without the EGFR-targeting drug cetuximab that is seeking to recruit patients with advanced bowel cancers is excluding those with *KRAS* mutations; official labelling for cetuximab and another drug that targets EGFR has lately been altered to reflect the change in recommended practice. Furthermore, *KRAS* tests are being widely marketed. Three papers in the *Journal of Clinical Oncology* that are in the Top Ten (#8) or hover outside that list (S. Khambata-Ford, *et al.*, 25[22]: 3230-7, 2007; total cites 174, latest count 36, at #13; and A. Lievre, *et al.*, 26[3]: 374-9, 2008; total cites 139, latest count 36, at #14) are being widely quoted because the data in them contribute significantly to accumulating evidence for this "step toward personalized medicine for patients with colorectal cancer" (Y. Jiang, *et al.*, *Cancer*, 115[16]: 3609-17, 2009). The most recent of this trio appeared in April, 2008, but the evidence keeps rolling in—see, for example, C. S Karapetis, *et al.*, from October of the same year (*New Engl. J. Med.*, 359[17]: 1757-65, 2008).

KRAS is a gene, the human homolog of the Kirsten rat sarcoma-2 virus oncogene, that is linked with cellular signalling pathways, including those involving EGFR itself. The drugs active against EGFR include cetuximab and panitumumab. Dr. Rafael G. Amado and colleagues (#8) tested for *KRAS* mutations as part of a randomized trial comparing panitumumab and best supporting care in patients with metastatic colon cancer. Any effect of the drug was limited to those with wild-type *KRAS*. In #13 the drug was cetuximab and other markers (two EGFR ligands) were studied but the result for *KRAS* was similar to #8's: patients whose tumors lacked *KRAS* mutations had significantly greater disease control from cetuximab. And a similar message emerged from the third paper (#14).

Might possession of a mutated *KRAS* by itself contribute to a poorer outlook for patients with advanced bowel cancer, irrespective of any treatment aimed at EGFR? Seemingly not. A presentation at this year's ASCO meeting (C. Fuchs, *et al.*, *J. Clin. Oncol.*, 27 [15s]: abstr 4037, 2009) drew on data from a chemotherapy trial starting 10 years ago and not involving EGFR-targeting agents. Possession of wild-type as opposed to mutated *KRAS* had no effect on disease-free or overall patient survival. A poster at a symposium on gastrointestinal cancers held during ASCO 2009 (V. Shankaran, *et al.*) provided an answer to a different question: Since *KRAS* testing is not cheap and since drugs like cetuximab are expensive, does a policy of not giving such drugs to those whose tumors are wild-type *KRAS* make sense in terms of economics as well as clinically? It seems that the cost of *KRAS* testing incident cases (estimated at $13 million a year for the US) is very much less than the savings made by not giving drugs predicted to be of no benefit to the recipient. A health economic analysis of a large Canadian trial, noting the daunting added costs involved when cetuximab is added to best supportive care alone, found the impact much reduced for patients with wild-type *KRAS* (N. Mittmann, *et al.*, *J. Natl. Cancer Inst.*, 101[17]: 1182-92, 2009).

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Molecular Location on chromosome 12: base pairs 25,249,446 to 25,295,120.

Medicine Top 10 Papers

Rank	Paper	Citations This Period (May-Jun 09)	Rank Last Period (Mar-Apr 09)
1	The ACCORD Study Group (H.C. Gerstein, *et al.*), "Effects of intensive glucose lowering in type 2 diabetes," *New Engl. J. Med.*, 358(23): 2545-59, 12 June 2008. [Writing Group: 10 U.S. and Canadian institutions] *311IJ	87	1
2	The ADVANCE Collaborative Group (A. Patel, *et al.*), "Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes," *New Engl. J. Med.*, 358(24): 2560-72, 12 June 2008. [Writing Group: 18 institutions worldwide] *311IJ	69	3
3	J. Yu, *et al.*, "Induced pluripotent stem cell lines derived from human somatic cells," *Science*, 318(5858): 1917-20, 21 December 2007. [Genome Ctr. Wisconsin, Madison; U. Wisconsin, Madison] *243HE	68	2
4	The ONTARGET Investigators (S. Yusuf, *et al.*), "Telmisartan, ramipril, or both in patients at high risk for vascular events," *New Engl. J. Med.*, 358(15): 1547-59, 10 April 2008. [Writing committee: 5 institutions worldwide] *285NK	57	†
5	B. Escudier, *et al.*, "Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomized, double-blind phase III trial," *Lancet*, 370(9605): 2103-11, December-January 2007. [15 institutions worldwide] *247DY	52	†
6	R.R. Holman, *et al.*, "10-year follow-up of intensive glucose control in type 2 diabetes," *New Engl. J. Med.*, 359(15): 1577-89, 9 October 2008. [6 U.K. institutions] *358FS	49	8
7	J.M. Llovet, *et al.*, "Sorafenib in advanced hepatocellular carcinoma," *New Engl. J. Med.*, 359(4): 378-90, 24 July 2008. [22 institutions worldwide] *329FK	45	†
8	R.G. Amado, *et al.*, "Wild-type *KRAS* is required for panitumumab efficacy in patients with metastatic colorectal cancer," *J. Clin. Oncol.*, 26(10): 1626-34, 1 April 2008. [Amgen, Thousand Oaks, CA; Ghent Univ. Hosp., Belgium; Univ. Hosp. Gasthuisberg, Leuven, Belgium; Ospedale Niguarda Ca' Granda, Milan, Italy] *281WY	44	†
9	K. Miller, *et al.*, "Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer," *New Engl. J. Med.*, 357(26): 2666-76, 27 December 2007. [9 U.S. and Canadian institutions] *245UO	42	10
10	E.S. Chung, *et al.*, "Results of the Predictors of Response to CRT (PROSPECT) trial," *Circulation*, 117(20): 2608-16, 20 May 2008. [13 institutions worldwide] *303PQ	42	†

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