Researchers also analyzed 611 plasma samples for 15 proteins that play a role in angiogenesis and the pathogenesis of colorectal cancer, uncovering potential prognostic indicators for treatment with regorafenib. High baseline concentrations of circulating tumor DNA were associated with shorter median survival, regardless of treatment. In patients who received regorafenib, high concentrations of circulating TIE-1 were associated with improved OS. Among those receiving a placebo, higher concentrations of IL8 and PlGF were associated with poorer OS.

“With a large cohort, this study confirms the concept that molecular tumor profiles change over time, and surveying the plasma provides insight into the molecular features of the tumor at any given point in the disease course,” says Scott Kopetz, MD, PhD, a colorectal cancer specialist at The University of Texas MD Anderson Cancer Center in Houston. Kopetz estimates that about 10% of patients with colorectal cancer at MD Anderson already receive such testing, but he anticipates that number will go up as clinicians become more comfortable with the technique and as additional uses for it emerge.

“The only drawback to this method is that our technology advances more rapidly than our ability to act on it,” says Lenz. “Finding a new mutation doesn’t mean that we immediately have a new treatment, and not every mechanism of resistance is based on gene mutations.”

Overstimulation Fatal for Cancer Cells

Many cancer drugs inhibit oncogenes, but no approved therapies use the opposite strategy of overstimulating them. However, Bert O’Malley, MD, of Baylor College of Medicine in Houston, TX, and colleagues now report evidence that this counterintuitive approach may work.

The researchers were hunting for inhibitors of steroid receptor coactivators (SRC), a family of proteins that enable steroid hormone receptors such as estrogen receptor and progesterone receptor to switch on genes. SRCs benefit cancer cells by speeding growth, turning up metabolism, and promoting tissue invasion and metastasis. While performing high-throughput screening on 359,484 compounds to identify SRC inhibitors, O’Malley and his team uncovered more than 100 compounds that stimulate SRC-1, SRC-2, and SRC-3. Instead of tossing these molecules out, the researchers investigated their effects and noticed that one of them, MCB-613, killed cancer cells.

As the team reported in August, MCB-613 proved lethal in several cancer cell lines, including breast, prostate, and lung, but spared healthy cells (Cancer Cell 2015;28:240–52). MCB-613 triggered a surge in reactive oxygen species in tumor cells and initiated the unfolded protein response, a pathway that cells activate when they are under stress.

To confirm that MCB-613 works by overstimulating SRCs, the researchers measured whether the promoters for two of SRC-3’s transcriptional targets were activated. Treating tumor cells with MCB-613 dramatically increased activity of both promoters. The effect was smaller in cells with reduced levels of all three SRCs.

The two most common causes of cell death—apoptosis and autophagy—weren’t responsible for the demise of the MCB-613–treated cells. Instead, O’Malley and colleagues determined that the compound triggers paraptosis, an uncommon form of cell death that can occur during embryonic development and neurodegeneration and in response to some anticancer drugs.

The researchers also tested MCB-613 in mice with breast tumors. After 7 weeks, tumor growth stalled in the 13 treated mice, whereas tumors tripled in volume in the 14 control animals.

A cancer cell can cope with the harsh conditions inside a tumor, but “it’s operating at its maximum compensation in terms of stress,” says O’Malley. By boosting levels of reactive oxygen species, MCB-613 might increase the amount of stress on cancer cells and push them over the edge. The study “shows that you can kill cancer cells by overstimulating an oncogene,” he says.

Potential side effects from this approach include driving normal cells to become cancerous and increasing the aggressiveness of any tumor cells that survive the treatment. O’Malley says that his team didn’t see any sign of these problems in their cell lines or animal studies.

“The concept that hyperactivation of an oncogene can be therapeutic is intriguing and worth further exploration,” says Myles Brown, MD, of Dana-Farber Cancer Institute in Boston, MA. However, he cautions that the researchers need to do more work on MCB-613 “to validate that SRCs are the only targets of its actions.”

Skin Cancer Drug Also Targets Brain Tumors

According to results from phase II studies conducted through the Pediatric Brain Tumor Consortium, a subtype of the brain stem tumor medulloblastoma may respond to vismodegib (Erivedge; Genentech)—approved for basal cell carcinomas—with less toxicity than current standard therapy. Both cancers arise from aberrant Sonic hedgehog (SHH) pathway activity; vismodegib inhibits a key protein, Smoothened (SMO), in this signaling cascade.

Medulloblastoma’s SHH subtype (SHH-MB) occurs in about 60% of adult and 25% of pediatric patients. Initial treatment involves a combination of surgery, radiation, and cytotoxic therapy, with a 5-year overall survival of 70%. However, patients are often left with severe long-term side effects, and a grim prognosis if the tumor recurs.

“We need a therapy that is less toxic and better honed to its target,” says corresponding author Giles Robinson, MD, a pediatric neuro-oncologist at St. Jude Children’s Research Hospital in Memphis, TN.

The studies enrolled 31 adults and 12 children respectively, all with recurrent or refractory medulloblastoma (J Clin Oncol 2015;33:2646–54). Following treatment with vismodegib, a total of 13 patients experienced prolonged disease stabilization for up to 16 months. Four of these patients had significant tumor shrinkage for longer than 2 months, while another four had shorter responses. All positive responses occurred in patients with SHH-MB, and none among those with non-SHH tumors. So “while vismodegib seems like a good drug with a huge amount of potential, it’s effective for only a select group,” Robinson notes.

Interestingly, the SHH-MB subtype didn’t guarantee sensitivity to SMO inhibition. Molecular analyses of 26
Overstimulation Fatal for Cancer Cells


Updated version  Access the most recent version of this article at: doi:10.1158/2159-8290.CD-NB2015-122

E-mail alerts  Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions  To request permission to re-use all or part of this article, use this link http://cancerdiscovery.aacrjournals.org/content/5/10/1010.1. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.