

CANCER RESEARCH

Can Fasting Blunt Chemotherapy's Debilitating Side Effects?

Asking a cancer patient to fast while undergoing chemotherapy may seem like adding insult to injury. But a dramatic experiment in mice has led some researchers to suggest that fasting may blunt the side effects of cancer treatment and perhaps even allow patients to tolerate higher drug doses. The idea is considered radical, even worrying, to some oncologists—especially because patients have already begun trying it on their own. Now, a clinical trial, in which patients undergoing chemotherapy for bladder and lung cancer will fast for as long as 3 days with only water to drink, is slated to begin in the next 2 months.

The strategy is the brainchild of Valter Longo, a gerontology researcher at the University of Southern California (USC) in Los Angeles who has long studied how calorie restriction extends life span in various species. Although the precise mechanism isn't clear,

it's widely believed that cutting calories slows the growth rate of cells and makes them more stress-resistant, protecting them from the cumulative damage of aging.

Longo wondered whether this effect might help protect healthy cells from chemotherapy, which kills rapidly dividing cells, whether normal or cancerous. In yeast, he found, most cells, as expected, became more stress-resistant when nutrients were dialed down. But yeast cells expressing genes similar to the oncogenes that help drive cancer did not react to calorie restriction; they kept on growing and dividing. Longo reasoned that in cancer cells "it's the oncogenes that regulate the stress resistance," and "those are always on," causing the cells to produce growth factors unaffected by calorie restriction.

Longo, along with cancer biologist Lizzia Raffaghello of the Gaslini Children's Hospital

in Genoa, Italy, USC graduate student Chaghan Lee, and their colleagues, tested this strategy in mice. Recognizing that cancer patients could not endure long-term calorie restriction, they tried a briefer but more extreme version: total fasting. Mice starved for 48 to 60 hours and then given high doses of a chemotherapy drug showed no visible signs of toxicity, yet many control animals died from the treatment. When the animals were injected with a neuroblastoma cell line, which mimics an aggressive pediatric cancer, the fasting combined with chemotherapy didn't

appear to blunt the treatment's effects on the cancer, suggesting that healthy cells were protected from chemotherapy by fasting but cancer cells were not.

To Rafael de Cabo, a researcher who studies aging at the National Institute on Aging branch in Baltimore, Maryland, the findings make sense. It's a hallmark of calorie restriction that animals "are much more resistant to any type of toxin," he says.

Longo's only publication so far on the subject appeared in late March in the *Proceedings of the National Academy of Sciences*, but "a lot of people are already doing it" on their own, he says. "Even though we were very clear, 'Don't try this at home,' I get an e-mail every day" from individuals interested in doing so.

One enthusiast is Thomas Cravy, a 66-year-old retired ophthalmologist in Santa Maria, California, who is battling metastatic prostate

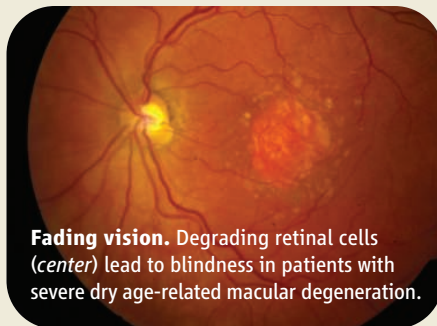
GENETICS

First Gene for Severe Dry Macular Degeneration

The past few years have been a bonanza for researchers hunting for genes that cause age-related macular degeneration (AMD), the disease that robs tens of millions of elderly people of their vision. Now comes the first report of a genetic variant linked to slightly higher risk for severe "dry" AMD, one of the two advanced forms of the disease. The results could eventually lead to a new treatment for macular degeneration. But the authors also have a second message: They say that their findings suggest a safety risk from using a therapy recently introduced to treat the other, so-called wet, form of AMD.

Some outside researchers, however, are skeptical of the new gene discovery, reported online this week in the *New Eng-*

land Journal of Medicine (NEJM). "It's an amazing result, but the excitement is tempered by the absence of an effect in other cohorts," or patient groups, says ophthalmologist and geneticist Albert Edwards of



Fading vision. Degrading retinal cells (center) lead to blindness in patients with severe dry age-related macular degeneration.

the Mayo Clinic in Rochester, Minnesota.

Advanced AMD involves loss of fine vision after age 60 in the center of the retina, or the macula. Patients with the wet type lose vision because blood vessel growth damages the macula; in the "dry" type, also known as geographic atrophy, light-sensing cells in the retina slowly die. At least three genes that steeply raise the risk of both types have been found by scanning the entire genome for disease markers (*Science*, 20 October 2006, p. 405).

The *NEJM* study, however, used an older approach. The researchers homed in specifically on genes for Toll-like receptors, proteins that recognize pathogens and signal the immune system to respond.

Probing the DNA of 825 Utah patients with AMD and about 360 healthy controls, a multi-institution team led by ophthalmologist and geneticist Kang Zhang of the University

cancer. Cravy just finished his third round of chemotherapy in 2 months, each combined with fasting. After the first round left him suffering some side effects, Cravy extended the time he fasts after treatment from about 8 hours to 24 hours, to go beyond the half-life of the most toxic drug; he also fasts for about 64 hours before treatment. Cravy now reports virtually no ill effects from chemotherapy. “On day five [after treatment] was the first time I played golf and walked the whole golf course,” he says. He admits that his mental sharpness fades during the 3½ days he fasts. But the approach has made him much more willing to try chemotherapy, which he had long resisted because he so feared its side effects.

The possibility that patients will try fasting before the approach has been properly tested “is exactly my fear,” says Leonard Saltz, an oncologist who specializes in colon cancer at Memorial Sloan-Kettering Cancer Center in New York City. “I still do fast on Yom Kippur,” he says, and those 24 hours without sustenance are a challenge. “Would I be enthusiastic about enrolling my patients in a trial where they’re asked not to eat for 2½ days? No.”

That, however, is exactly what Longo and



Radical notion. Valter Longo is testing whether fasting can protect cancer patients from chemo’s toxicity.

clinical colleagues at USC are gearing up to do. David Quinn, a genitourinary oncologist at USC, is preparing with Longo and others to recruit 12 to 18 bladder and lung cancer patients who will fast for 24, 48, or 72 hours before and just after chemotherapy. They will begin gradually, with 24 hours of fasting, before ramping up. If the fasting appears safe and potentially effective, the group will recruit another 42 patients, 14 of whom will not fast. Everyone will receive the same chemotherapy regimen. The work is funded by USC and the V Foundation for Cancer Research, an advocacy group that funds many mainstream cancer studies.

Quinn hopes fasting will not only minimize chemotherapy’s toxicity but also make cancer cells more susceptible to chemotherapy. Hints of such increased effectiveness appeared in the mouse data, but the clinical trial will be too small to test this hypothesis.

“It’s reasonable enough to at least look at it in a small number of patients,” says Alan Sandler, an oncologist who treats lung cancer at Vanderbilt University in Nashville, Tennessee. “But it really goes against a lot of the thoughts that people have, that you need to eat to feel better.”

—JENNIFER COUZIN

of California, San Diego, identified a single-base glitch in the gene for Toll-like receptor 3 (TLR3) that modestly raises the risk of advanced AMD. They also found this association in two other groups of patients of European descent.

TLR3 recognizes double-stranded RNA from viruses and tells infected cells to die. To explore how this might cause macular degeneration, Zhang’s team injected the eyes of mice carrying two copies of the protective variant with double-stranded RNA. Fewer retinal cells died than did cells in mice that lacked the variant. In patients without any protective copies, a viral infection in the eye might push TLR3 into overdrive so that it keeps killing retinal cells, they suggest.

A small molecule that blocks TLR3 might slow the disease in patients with dry AMD, says Zhang. But the news could be bad for an experimental therapy for wet AMD: adding

double-stranded RNA to cells to block a specific gene to prevent the formation of blood vessels. Although this RNA interference therapy may slow wet AMD, it could also spur some patients to develop the dry form. “It’s a cautionary note,” says Zhang.

That’s assuming that the results hold up. Edwards and others published a paper last April that did not find a significant association with the same TLR3 variant in two cohorts with AMD. Geneticist Rando Allikmets of Columbia University also hasn’t seen the link in five cohorts he’s studying. But geneticist Nicholas Katsanis of Johns Hopkins University in Baltimore, Maryland, a co-author of the *NEJM* study, says one key difference is that their controls had “squeaky-clean retinas” without even a trace of macular degeneration. He hopes other investigators will reanalyze their data using the same strict criteria.

—JOCELYN KAISER

EPA Is Going Down the Drain

The U.S. Environmental Protection Agency (EPA) is taking a closer look at the health or environmental impact of pharmaceuticals and personal care products that get flushed down the toilet. Earlier this month, the agency asked for public comment on its plans to collect data from hospitals and nursing homes. The agency has also asked the U.S. National Academies to run a 2-day workshop in December about possible ways to assess the risk to human health when the drugs get into drinking water. Meanwhile, EPA is revising its procedures to account for the effects of disposed drugs on aquatic life. The potential impact on health of these chemicals “is definitely a big deal,” says environmental scientist G. Allen Burton of Wright State University in Dayton, Ohio. “It’s gratifying to see EPA moving ahead with this.”

—ERIK STOKSTAD

National Medals Awarded

Three physicists, two biologists, a chemist, a computer scientist, and an electrical engineer have received the 2007 National Medal of Science, the U.S. government’s highest scientific honor. Most already have a bagful of laurels, including Andrew Viterbi, the father of wireless communications, and molecular biologist Robert Lefkowitz, who in recent years has won the \$1 million Shaw Prize for his work on cell receptors. As in previous years, men predominate. Nuclear physicist Fay Ajzenberg-Selove is the only woman, joining Mustafa El-Sayed, Leonard Kleinrock, Bert O’Malley, Charles Slichter, and David Vineland as the other laureates.

The White House last week also named the winners of the 2007 National Medal of Technology and Innovation, including two California-based companies—eBay and Lockheed Martin’s Skunk Works—and six individuals.

—YUDHIJIT BHATTACHARJEE

Climate Call

A coalition of U.S. organizations that study climate and weather want presidential candidates John McCain and Barack Obama to bolster U.S. climate science efforts once in office. In a 12-page document released last week, the groups advocate more research funding and computing resources for climate change studies, including a strengthened emphasis on the societal impacts of “severe weather and climate change.” They back a report issued last year by the National Research Council that called on the government to commit a total of roughly \$7 billion through 2020 for Earth-observing systems.

—ELI KINTISCH