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Drug may be near for cancer's companion condition cachexia

Cachexia is the muscle wasting and weight loss that often accompany cancer's effects. Two potential treatments that may boost muscle strength are in Phase 3 clinical trials.

By Amber Dance, Special to the Los Angeles Times

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Bonnie Addario didn't even know there was a word for what was happening to her. As if lung cancer weren't bad enough, the 54-year-old had lost 30 pounds off her normally 130-pound frame. Her life was limited to her husband's Barcalounger, where she had to recline because she lacked the strength to sit up straight. "It affected everything I did," says Addario, who is alive and well nine years later in San Carlos, Calif. "I literally could not get up and down the stairs."

There is a name for what Addario experienced: cachexia. It is the muscle wasting and weight loss that are so often cancer's sidekick.

Doctors and patients have long assumed cachexia is an integral part of cancer, and it's rarely discussed. "Ninety percent of oncologists completely ignore the cachexia because there's no known therapy," says Alfred Goldberg, a professor of cell biology who studies protein and muscle breakdown at Harvard Medical School in Boston.

But that could soon change as two potential cachexia treatments are now in Phase 3 clinical trials. If studies continue to go well, the drugs could become available for lung cancer patients within the next two to three years.

The main goal of both medications is to give people more muscle strength as they fight cancer. But they may do even more, scientists hope.

"It's not clear that if you treat cachexia you will prolong life," says Dr. Egidio Del Fabbro, a palliative care physician at the University of Texas M.D. Anderson Cancer Center in Houston, but "we suspect it will." Del Fabbro is not involved with either of the companies developing the drugs, GTx Inc. of Memphis, Tenn., and Helsinn Therapeutics Inc. of Bridgewater, N.J.

Cachexia (pronounced kuh-KEK-see-uh) is commonly defined as the unintentional loss of 5% or more of a person's weight within a six-month period. Crucially, it's muscle that slides off one's frame, often with fat as well. It's associated with advanced cancers as well as HIV, heart failure and kidney disease. In layman's terms, it means "the patient looks awful, they look weak, they've lost much of their body mass," Goldberg says.

Cachexia is especially prevalent in pancreatic and lung cancers. People with the condition also tend to lose their appetites, but eating more does not help because the body's metabolism is operating at a higher-than-normal rate, says Vickie Baracos, a metabolism researcher at the University of Alberta in Edmonton.

"The controls are not operating properly," she says. "It's sort of like having your thermostat turned up and the window left open at the same time."

Given current rates of obesity, muscle wasting is sometimes hidden behind a layer of fat. "You can have somebody who technically looks obese, but they have the muscle mass of a concentration camp victim," says Dr. Mitchell Steiner, a urologic oncologist who co-founded GTx and now serves as the company's chief executive.

In the past, researchers have focused on destroying cancer. But now that many people survive, or live longer with cancer, some scientists are shifting their focus to medicines that improve the quality of life for patients, says Melinda Sheffield-Moore, a muscle physiologist at the University of Texas Medical Branch at Galveston.

Cachexia has a huge, and detrimental, effect on quality of life.

Dr. Richard Gralla, a medical oncologist at Hofstra University in New York City, has conducted two surveys of about 4,000 cancer patients and their caregivers; 83% of the patients reported that nutrition, loss of appetite and weight, and fatigue were "very important" or "important" concerns.

"This was among the very top issues for patients," says Gralla, who presented his survey results at the annual meetings of the American Society of Clinical Oncology in June and the San Antonio Breast Cancer Symposium in December. (He has also consulted for GTx.) The weight loss is more than an inconvenient side effect. "Cancer kills, but cachexia can also kill if you lose a significant amount of muscle," Sheffield-Moore says. Weakened heart muscles might give out, the muscles needed to breathe may not perform adequately or general weakness can make a person susceptible to infections, she says.

In addition, wasting and weakness make it harder for a person to withstand the toxic effects of chemotherapy and radiation, so it may cut short treatment. Cachexia is a bad sign for recovery as well. "It sort of tells us that the cancer's winning," Sheffield-Moore says. Scientists are just starting to understand the biology of cachexia. Part of the problem appears to be that cancer and its treatments create inflammation — normally a healthy response to disease — but for some reason it goes haywire and triggers the muscle breakdown.

There are several treatment options for cachexia, but "lack of success is the norm," says Dr. Ronald Natale, director of the lung cancer clinical research program at Cedars-Sinai's Samuel Oschin Comprehensive Cancer Institute in Los Angeles. He says the most commonly used drug is Megace, an appetite stimulant also given to people who have cachexia due to AIDS. It can make people want to join their families around the dinner table again, but the weight gained is mostly fat and water, not the much-needed muscle, Natale says.

Marijuana or its pharmaceutical equivalent, Marinol, is also an option to boost appetite, but the effects don't tend to last long, Natale says. Some doctors try testosterone, since it builds up muscle. However, it has unpleasant side effects such as hair growth and sweating, and increases prostate cancer risk in men.

GTx developed a chemical that acts like testosterone but is specific for muscle growth, so it doesn't trigger the side effects. In an early

trial, 159 people with various cancers received the drug, enobosarm, or a placebo in addition to their normal cancer treatment. Those who took enobosarm for four months held on to their muscle and even gained a few pounds — the equivalent of a "50-ounce steak," Steiner says. They were also better at climbing a dozen stairs. For the average-sized person, the improvement would be akin to toting an extra 13 pounds up the steps, he says. GTx presented the results at cancer meetings in 2009 and 2010.

GTx is now testing enobosarm in two trials, each involving 300 patients with non-small cell lung cancer, the most common type of lung cancer. Lung cancer is the biggest cancer killer and frequently comes with severe cachexia. Steiner expects results in 2013 and, if all goes well, predicts the drug could be available at the beginning of 2014. He envisions enobosarm being prescribed not only to treat cachexia but also to prevent or delay the wasting.

GTx's approach is exciting, says Del Fabbro of M.D. Anderson, as is that taken by Helsinn. That company's drug, anamorelin, is designed to mimic the effects of the "hunger hormone" ghrelin, which boosts appetite, builds muscle, pushes food through the digestive system and cuts inflammation.

More than 300 people with cancer have taken anamorelin for up to three months, says Dr. John Friend, a family medicine physician and senior vice president for research and development at Helsinn. They gained weight and reported improved quality of life on questionnaires. Helsinn reported early trial results at an oncology meeting in 2007.

Helsinn is now enrolling about 950 people in two trials, which Friend expects to complete in 2013. With good results, he hopes Helsinn could release the drug in 2015 or 2016. If they are successful with non-small cell lung cancer, Helsinn and GTx are interested in expanding their drugs to other cancers and cachexia conditions.

The most exciting approach to cachexia is to interfere with the biological systems directly causing it, Natale says. For example, natural body chemicals called myostatin and activin normally prevent muscle buildup. Some researchers hope to treat muscle loss with drugs that sponge up myostatin or activin.

As reported in a 2010 study in the journal *Cell*, scientists from Amgen Research in Thousand Oaks reversed muscle wasting in cancer-ridden mice using a medicine that sticks to activin, preventing it from acting on muscle. Harvard's Goldberg, who worked on the study, was excited to see that not only did the treatment reverse the low appetite and weight loss but also "the animals lived much longer, despite having an enormous tumor," he says. (Amgen declined to comment on any further work.)

It's too early to say whether people, like the mice, would live longer if their cachexia were controlled with medication. Gralla would be happy if the drugs just make the time they have more enjoyable; increasing survival would be a "bonus," he says. health@latimes.com