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HEALTH AND BEHAVIOR

Cancer fighters target blood flow to tumors

Reaching final testing, 'massive wave' of drugs offers hope for patients to live longer, better

By Anita Manning
USA TODAY

ATLANTA — A category of experimental cancer-fighting drugs designed to cut off a tumor's blood supply and starve it is moving closer to reality, raising hopes among doctors and patients desperate for effective weapons to halt cancer's spread.

Among thousands of abstracts on cancer treatments presented here this week at a meeting of the American Society of Clinical Oncology were more than 50 studies on 19 of these "anti-angiogenic agents" — so named for their ability to impede blood vessel creation — including green tea extract and shark cartilage.

Five of the drugs are in the latest stages of testing and could be on the market within two years.

"Only in the last five years have we begun to understand the natural angiogenesis inhibitors," says internist William Li, president of the Angiogenesis Foundation, a nonprofit research and education organization.

About a dozen of these natural inhibitors have been identified, including angiostatin and endostatin, which are being developed by pharmaceutical companies. Neither has been used in humans, but EntreMed of Rockville, Md., says it will begin human trials of its endostatin drug this year in Boston.

Drug companies have about 40 anti-angiogenic drugs in human tests — "a massive wave of development," Li says.

Among the findings presented this week are the first from studies that used combined chemotherapy and anti-angiogenic therapy, an approach thought to be highly promising, Li says.

"Lab research for the last several years has been showing us it's possible to amplify the tumor-killing effects of standard drugs by adding an anti-angiogenesis drug," he says.

Researchers at New York University Medical Center on Sunday presented the first study of chemotherapy in conjunction with thalidomide — an anti-angiogenesis agent notorious for its role in causing birth defects in the early 1960s — to treat patients with the deadliest form of brain cancer, glioblastoma multiforme.

Enrolled patients had completed first-line treatment, but tumors recurred.

In such patients, the prognosis is not good, but "we have a reasonably high response rate," says researcher Jon Glass, who presented the study. "Out of 53 people we can assess for effectiveness of this treatment, 38 had some kind of response — either the tumor stopped growing or the tumor shrank."

Many patients "had a prolonged response duration after they stopped chemotherapy and we just had them on thalidomide," he says. Median survival was 42 weeks from diagnosis. "That's much longer than you'd see with standard therapy, where the average life expectancy is four months."

Chemotherapy acts to stop the cancer cell from dividing, Glass says.

"What we did was to attack it from a completely different angle, to block the signal the cell sends out to form new blood vessels," he says. "We hope that by giving chemotherapy and anti-angiogenesis agents, we will not only stop tumor cells, but will also prevent cells that get by the chemotherapy from signaling to form new vessels."

It may be that anti-angiogenic therapies will be used not to cure cancer but to keep it from spreading until other drugs are available to kill the tumor.

> "What we think anti-angiogenesis medication will do will be to provide disease stabilization, to slow the tumor growth and hold it in check."
> — Researcher Jon Glass

"If a cancer patient comes to me and they've got a big tumor growing rapidly and metastasizing, we traditionally cut it out and give chemotherapy or radiation. Most of the time, that's not successful," Glass says.

"What we think anti-angiogenesis medication will do will be to provide disease stabilization, to slow the tumor growth. . . . Whether you're a cancer patient or an oncologist, if we are able to stabilize the cancer, it's a win."

Often, even though life is not extended, it is improved.

"You can buy extra time in terms of quality of life," he says. "Stability of disease, not necessarily disappearance of disease, can be a desirable goal of anti-angiogenic therapy for cancer, because even if you don't survive longer, you may survive better. That's very important for cancer patients."

For more information, call the Angiogenesis Foundation at 617-576-5708 or see the Web site at www.angio.org.

Tumors probably pop up in all adults all the time

Angiogenesis is a natural process of blood vessel growth that normally stops in adulthood, except for the purpose of wound healing and during pregnancy and menstruation.

Cancer cells turn on the process to create a source of nutrients that will allow them to divide and grow into tumors.

"In the adult body, we probably are springing up tumors all the time," says internist William Li, president of the Angiogenesis Foundation in Cambridge, Mass. "But tumor cells can't grow beyond 2-3 millimeters, the size of a small BB, because they don't have a blood supply."

In normal adult tissue, angiogenesis is turned on by the release of growth factors, then halted by production of natural angiogenesis inhibitors.

"It's an on-off switch," Li says.

But cancer tricks the body's normal angiogenesis controls with "an unrelenting release of growth factors that overwhelms the inhibitors," he says.

"Once new vessels invade the cancer cell, the tumor is brought oxygen and nutrients and is able to grow rapidly," Li says. "The blood vessels provide exit channels for the cancer cells to move around the body, called metastases."

By the time a tumor has grown large enough to be felt, it is usually about 1 centimeter in size, about the size of a small grape, he says.

A tumor that size is packed with blood vessels. "So by the time most doctors pick up cancer, angiogenesis has already occurred," Li says.

By then, it is shedding 1 million cancer cells into the system in 24 hours, he says, "but the immune system knocks them out, so of the million, only one survives. That one cell will lodge in an organ and stay there. It may divide, but it can only grow to 2 millimeters in size without new blood vessels. It will remain undetectable until it can unleash its own wave of angiogenesis."

Targeting tumor growth

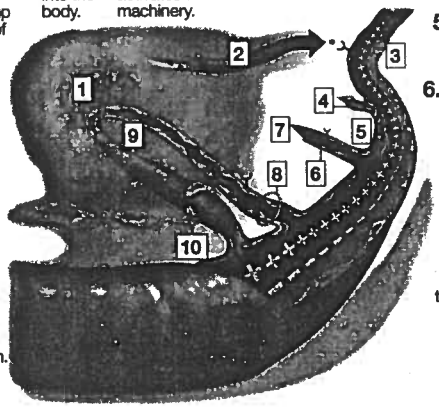
For a cancerous tumor to grow, it needs to create its own blood supply. It does this by a 10-step process called angiogenesis. Drug companies looking for ways to combat tumor growth are creating drugs that target each of these steps:

1. Production by the tumor of proteins called angiogenic factors — growth factors that induce blood vessel growth. Tumors pump out large quantities of this substance and release it in a big cloud around them.

2. The growth factor is released into the body.

3. The growth factor binds to special receptors located on the cells of blood vessels (endothelial cells). This activates the cell's internal machinery.

4. Once activated, the endothelial cells release enzymes that dissolve holes in the wall of the existing blood vessel, to allow new blood vessels to emerge.



5. The endothelial cells divide and multiply.

6. The divided cells begin to migrate toward the tumor through the holes created in the blood vessel wall.

7. As these blood vessel cells migrate forward, they dissolve the tissue in their path.

8. The blood vessel cells form individual tubes (sprouts).

9. The individual sprouts connect to form a loop of newly formed blood vessels for circulation.

10. The newly formed blood vessels are stabilized by specialized muscle cells.

Source: The Angiogenesis Foundation

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