Anti-angiogenesis Treatment

The search for better cancer drugs

Today we are better able to treat cancer than ever. More than half of all people with cancer now live at least 5 years after being diagnosed. This progress is the result of better ways to find cancer early and better ways to treat cancer once it is found.

But cancer treatment is still far from perfect. Many cancers cannot be cured, and some are still very hard to treat. The treatments we use, like chemotherapy, can sometimes cause severe side effects that can affect a person's quality of life. Patients and doctors have long hoped for cancer treatments that would work as well or better than the ones we use now but with fewer side effects.

Scientists have learned a great deal in recent years about what makes cancer cells different from normal cells in the body. This has helped them find *targeted drugs* - drugs that focus on the cancer cells without having major effects on normal cells in the body. The American Cancer Society has funded the search for such treatments for many years.

One promising cancer treatment to come from this research is called *anti-angiogenesis* (an-tee-an-jee-oh-**jen**-uh-sis) treatment.

What is anti-angiogenesis treatment?

Angiogenesis is the process of making new blood vessels. The term comes from 2 Greek words: *angio*, meaning blood vessel, and *genesis*, meaning beginning.

In most cases, this is a normal, healthy process. As the human body grows and develops, it needs to make new blood vessels to get blood to all of its cells. As adults, we don't have quite the same need for making new blood vessels, but there are times when angiogenesis is still important. New blood vessels, for instance, help the body heal wounds and repair damage.

But in a person with cancer, this same process creates new, very small blood vessels that give a tumor its own blood supply and allow it to grow.

Anti-angiogenesis is a form of targeted therapy that uses drugs or other substances to stop tumors from making new blood vessels. Without a blood supply, tumors can't grow.

Why do cells need blood to survive?

All of the parts of your body, such as the skin, muscles, and organs, are made up of billions of cells. Every cell must have a constant supply of blood to live. Blood carries vital substances like glucose (sugar), minerals, and oxygen to the cells. And it carries away the waste products. Without blood, cells would quickly die.

Blood vessels are the pipelines that carry blood throughout your body. Major organs such as the heart, lungs, and liver are supplied by large blood vessels (arteries and veins) that run directly to and from those organs. Smaller blood vessels branch out from the larger ones. The smallest branches, called capillaries, supply individual cells.

Normal cells are supplied with blood by vessels that grow as your body develops. As organs grow larger, the blood vessels that supply them grow too, allowing them to carry more blood to the cells making up those organs.

Why do tumors need their own blood supply?

A tumor starts from a single cell that has become cancer and is dividing to make more cancer cells. At first these cells can use the nearby blood vessels, but as the tumor grows, the cells in the middle of the tumor get farther away from the blood supply. For the tumor to go on growing, it must have new blood vessels. Without new blood vessels, a tumor can't grow larger than about the size of a pin head (about 1 to 2 cubic millimeters).

Tumors and new blood vessels support each other's growth

The cells that make up the lining of blood vessels are called *endothelial cells*. Cancer cells release chemicals that cause angiogenesis by prompting the endothelial cells to grow, divide, and make new blood vessels. Many different substances seem to cause angiogenesis.

As more blood vessel cells are made, the tumor cells and the blood vessel cells feed each other's growth. The blood vessels bring needed nutrients allowing the tumor to grow. At the same time, the tumor cells release their chemical messengers directly into the blood. This causes more blood vessels to be made to support more tumor growth.

How anti-angiogenesis drugs work

Anti-angiogenesis drugs don't attack cancer cells directly. Instead, they target the blood vessels the cancer cells need to survive and grow. By doing this, they may help prevent new tumors from growing. They may also make large tumors shrink if their blood supply is cut off.

Scientists have found a number of different pathways that cancer cells can use to cause blood vessel growth. Each step in these pathways is a possible target for cancer treatment. Different drugs may work at different steps in these pathways.

For example, one of the most important proteins in new blood vessel growth is vascular endothelial growth factor (VEGF). This protein is not made in large amounts by normal cells, but some cancer cells make it and release it into the area around them. VEGF then attaches to a protein (called the VEGF receptor, or VEGFR) on the surface of nearby endothelial cells. This signals the cells' control centers, to start growing and forming new blood vessels.

Many of the anti-angiogenesis drugs used today attack the VEGF pathway. Bevacizumab (Avastin®) was the first drug targeted at new blood vessels to be approved for use against cancer. It is a monoclonal antibody -- a man-made version of an immune system protein -- that binds to VEGF and keeps it from reaching the VEGF receptor. Other drugs, like sunitinib (Sutent®) and sorafenib (Nexavar®), are small molecules that attach to the VEGF receptor itself, keeping it from being turned on and making new blood vessels.

Drugs that target other blood vessel pathways are now being tested.

Some drugs already used to treat cancer have been found to affect blood vessel growth, too. But it's not clear how they work. For example, doctors have found that some chemotherapy drugs, if given around the clock in low doses, may prevent tumor growth without causing the serious side effects that higher doses would. Some research suggests the drugs may work because they stop the growth of endothelial cells.

Some other drugs used to treat cancer, such as thalidomide (Thalomid®) and lenalidomide (Revlimid®), are also known to affect blood vessel growth. But they work against cancer in other ways, too.

How anti-angiogenesis drugs differ from other cancer treatments

In some ways, anti-angiogenesis treatment is like chemotherapy. Both are forms of systemic treatment. This means that both treatments use drugs that travel throughout the body to have their effects. But anti-angiogenesis drugs do not work the same way chemotherapy does. Because of this, they differ in terms of what side effects they may cause and how well they work.

Side effects

For the most part, anti-angiogenesis drugs tend to have milder side effects than chemotherapy drugs.

Chemotherapy drugs work by attacking cells in the body that grow and divide quickly. This is why they work against cancer cells. But they can also harm other cells that divide quickly, such as those in the bone marrow, the skin, and in the mouth and intestines. This can lead to serious side effects like low blood cell counts (which can cause tiredness, infections, and bleeding), hair loss, mouth sores, nausea, and diarrhea.

Unlike chemotherapy drugs, anti-angiogenesis drugs do not harm these normal cells. They act where new blood vessels are forming, so they usually do not cause these kinds of side effects.

But anti-angiogenesis drugs are not risk-free and do have their own side effects. Although they're not as common or severe as those from chemotherapy, they can still be serious, or even life-threatening. Because anti-angiogenesis drugs are fairly new, it's not yet clear if the effects seen so far will be seen with all of these drugs.

Bleeding or holes in the digestive tract

Most anti-angiogenesis drugs have been shown to raise the risk of internal bleeding or of developing a hole in the digestive tract (stomach or intestines). In rare cases, this has been serious or even fatal. In people with a history of bleeding problems, with certain types of cancers, or with cancers in certain locations, the risks of using these drugs might outweigh the benefits.

Raised blood pressure

It's not clear why, but some of these drugs raise blood pressure. This problem is rarely serious and it seems to respond well to blood pressure medicines. Still, some people who have a history of high blood pressure, heart disease, or stroke may need to be watched closely or may not be able to take these drugs.

Surgery risks

Because they may affect wound healing, anti-angiogenesis drugs may need to be stopped before surgery or not started until a few weeks after surgery. This is to make sure blood vessels that are cut are able to repair themselves.

Pregnancy risks

These drugs might also affect a developing fetus. They will probably not be used for women who are pregnant or might become pregnant.

How anti-angiogenesis drugs affect tumors

Because chemotherapy and anti-angiogenesis drugs don't affect the same parts of the body, they can sometimes be given together.

When chemotherapy drugs work, they often cause tumors to shrink a lot, sometimes even making them disappear. But anti-angiogenesis drugs don't seem to work in the same way. In some cases they shrink tumors, but in others they just seem to stop them from growing any larger. (This is probably because the tumors have already grown some blood vessels.) Although this may help some people, it's not yet clear how long patients need to keep taking these drugs to keep the tumors from growing. Some patients may need long-term or maybe even life-long treatment.

Newer approaches that combine anti-angiogenesis drugs with chemotherapy, other targeted drugs, or radiation may work better than using them alone. For instance, early studies that tested the drug bevacizumab (Avastin) by itself did not find that it helped people with cancer to live longer. But later studies found that when it was used along with chemotherapy to treat certain cancers, it helped people live longer than if they got the chemotherapy alone.

Doctors aren't sure why this is the case. One theory is based on the fact that chemotherapy drugs may have a hard time getting to cells in the middle of tumors. Tumor blood vessels grow in a short amount of time and in an abnormal environment, so they are not as well-made and as stable as normal blood vessels. Because of this, they tend to be leaky. This affects how well drugs can reach the inside of the tumor. The theory is that bevacizumab may somehow stabilize these tumor blood vessels for a short period of time, allowing the chemotherapy to reach more tumor cells and be more effective. Research in this area is ongoing.

How well they work in different cancer types

Chemotherapy drugs can be useful in treating many types of cancer, but some cancers do not respond well to them. In some cases, anti-angiogenesis drugs may prove to be a better option.

For example, chemotherapy isn't helpful against kidney cancer. But doctors have long known that kidney tumors tend to form many blood vessels. Anti-angiogenesis drugs, such as sunitinib (Sutent) and sorafenib (Nexavar), have been shown to be useful against this type of cancer. Many doctors now consider these drugs to be the best treatments when systemic therapy is needed.

Because of the way anti-angiogenesis drugs work, they are only useful in treating cancers that form tumors. They won't work against blood cancers like leukemias.

Research in anti-angiogenesis treatment

Anti-angiogenesis research began more than 35 years ago with the work of the late Judah Folkman, MD. The ACS supported Dr. Folkman's research early in his career. Dr.

Folkman's early focus was on substances made by the body itself to curb blood vessel growth. Although several substances were found, for the most part they have not yet been shown to be useful as drugs.

But many man-made compounds that affect blood vessel growth have been created. Some are being studied in the lab or in clinical trials (see below), and some are already being used in doctors' offices.

Several hundred clinical trials of anti-angiogenesis drugs are now under way. While not all of these drugs will prove to be useful against cancer, many will help give patients more options for treatment.

How new drugs are tested

A new drug is first tested on cancer cells grown in lab dishes (cell culture studies). If the drug kills the cells or slows their growth enough, testing is done to see if the drug works in animals with cancer. A drug that seems to be safe and effective in animals may then be tested in humans in clinical trials, which are usually carried out in 4 phases.

Phase I clinical trials: The purpose of a phase I study is to find out how safe a new treatment is and to find the best dose for future studies. Doctors watch patients carefully for any harmful side effects. They start by giving very low doses of the drug to the first few patients and increase the dose for later groups of patients. This is done until the desired effects are seen or until serious side effects appear. Although doctors are hoping to help patients, the main purpose of a phase I study is to test the safety of the drug.

Phase II clinical trials: These studies are designed to see if the drug works. Patients are given the best dose of the drug as determined from the phase I study and closely watched for an effect on the cancer. The doctors also look for side effects.

Phase III clinical trials: Phase III studies have large numbers of patients -- usually hundreds. One group (the control group) gets the current standard (most accepted) treatment. The other group gets the new treatment. All patients in phase III studies are closely watched. The study is stopped if the side effects of the new treatment are too severe or if one group has a much better result than the others.

Phase IV clinical trials: Once a drug has been approved by the FDA and is available for all patients, it is still studied in other clinical trials (sometimes called phase IV studies). This way more can be learned about short-term and long-term side effects and safety as the drug is used in larger numbers of patients with many types of diseases. Doctors can also learn more about how well the drug works, and if it might be helpful when used in other ways, such as along with other treatments.

Please see our document, *Clinical Trials: What You Need to Know* if you want more information.

How anti-angiogenesis drugs are used today

When potential anti-angiogenesis drugs were first tested in the lab in the late 1990s, there was a lot of hype around them. The initial hope was that these drugs might replace chemotherapy, offering a more effective, less toxic way to treat cancer. But early study results in people did not live up to this hype. The drugs slowed cancer growth in some cases, but they didn't make tumors shrink or disappear.

We now know that the first drugs tested weren't very effective. We have also learned that there are many chemicals that can prompt new blood vessel growth, and cancer cells may be able to make more than one of these. Blocking just one growth pathway may not be enough.

Today doctors are more realistic about the role these drugs may have in treating cancer. Perhaps the greatest value of the anti-angiogenesis drugs is that they offer another option for some people with cancer. This is especially important for those who have limited treatment options. These drugs may not cure cancers by themselves, but they may help control its growth, or even cause some tumors to shrink.

What's more, some of these drugs have been shown to work well when given along with chemotherapy, helping people to live longer overall. These drugs may prove to be most useful when given with other forms of treatment.

The first anti-angiogenesis drug approved by the Food and Drug Administration (FDA) to treat cancer was bevacizumab (Avastin) in 2004. It is now used with chemotherapy to treat some types of cancer. Several other anti-angiogenesis drugs have since been approved.

Some of the newer anti-angiogenesis drugs also attack the cancer cells themselves. Researchers continue to get better at designing new drugs with multiple effects on cancer cells, which may make them even more effective. In the future, such drugs may blur the line between anti-angiogenesis drugs and other forms of cancer treatment.

The future of anti-angiogenesis treatment

Researchers are now looking at many different aspects of anti-angiogenesis drugs. Better understanding of these drugs will probably make them a bigger part of cancer treatment in the future.

Figuring out how to best use these drugs

Several anti-angiogenesis drugs are now used to treat cancer, and others will be in the near future. Because these drugs are still new, many questions about them have not yet been answered. Do they work better when used alone or with other treatments? What's the best way to give them? How long should they be given? These and other important questions are now being studied in clinical trials.

Finding new drugs

As researchers learn more about the process of angiogenesis and its effects on tumor growth, they will be able to develop newer, better drugs to attack this process. Some of these new drugs will also target the cancer cells themselves.

Vascular disrupting agents (VDAs)

Also called vascular targeting agents (VTAs), these are a related group of drugs that may prove to be important in treating cancer. Anti-angiogenesis drugs stop new blood vessels from forming, but is there a way to attack tumor blood vessels that have already formed?

Researchers have found differences between normal blood vessels in the body and those that supply tumors. Some new drugs may be able to exploit these differences, attacking tumor blood vessels but leaving normal blood vessels alone.

Several VDAs are now being studied in clinical trials. Early studies have shown that these drugs seem to work best on the inner parts of tumors. This may mean they will work well when used with other treatments that are more likely to work on the outside of the tumor, such as chemotherapy.

Combining anti-angiogenesis drugsIt is now clear that tumors can make and release many chemicals that can start angiogenesis. Using a drug that targets only one of these chemicals may not have a large effect on the cancer, but combining drugs that attack different targets may prove to be more useful. Studies combining these drugs are now under way.

Combining angiogenesis with other treatments

Anti-angiogenesis drugs tend to have milder side effects that are different from other cancer treatments. This makes the idea of combining them with other types of treatment very appealing. Researchers are now combining these drugs with chemotherapy drugs, radiation therapy, or other types of targeted therapies. Early study results have been promising.

Using metronomic chemotherapy

Most chemotherapy drugs were designed to attack cancer cells directly. But doctors have found that some of them may be useful as anti-angiogenesis drugs, too. When they are given at low doses over a longer period of time they seem to work without causing major side effects (as opposed to giving high doses at regular intervals, which is how they are usually used).

This approach is known as metronomic chemotherapy. Some evidence suggests that when used this way, the chemotherapy may be acting on the tumors' blood vessels. Studies are being done to test the value of metronomic chemotherapy, either alone or combined with anti-angiogenic drugs.

Additional resources

More information from your American Cancer Society

We have selected some related information that may also be helpful to you. You can find these on our Web site or order them from our toll-free number (1-800-227-2345).

Chemotherapy - What It Is, How It Works

Gene Therapy

Immunotherapy

Oncogenes and Tumor Suppressor Genes

Oral Chemotherapy: What You Need to Know

Questions That People Ask about Cancer (also available in Spanish)

Targeted Therapies

Understanding Chemotherapy: A Guide for Patients and Families (also available in Spanish)

Along with the above, the American Cancer Society has information about many different types of cancer and how they are treated.

National organizations and Web sites*

Along with the American Cancer Society, other sources of information include:

The Angiogenesis Foundation
Telephone number: 1-617-576-5708
Web site: www.angio.org

National Cancer Institute
Toll-free number: 1-800-4-CANCER (1-800-422-6237)
Web site: www.cancer.gov

This site includes a picture presentation of how angiogenesis works:
www.cancer.gov/cancertopics/understandingcancer/angiogenesis

**Inclusion on this list does not imply endorsement by the American Cancer Society.*

No matter who you are, we can help. Contact us anytime, day or night, for cancer-related information and support. Call us at **1-800-227-2345** or visit www.cancer.org.

References

Fidler IJ, Langley RR, Kerbel RS, Ellis LM. Angiogenesis. In: DeVita VT, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology*. 7th ed. Philadelphia, Pa: Lippincott Williams & Wilkins 2005:129-137.

Folkman J, Heymach J, Kalluri R. Tumor angiogenesis. In: Kufe DW, Bast RC, Hait WN, Hong WK, Pollock RE, Weichselbaum RR, Holland JF, Frei E, eds. *Cancer Medicine 7*. Hamilton, Ontario: BC Decker, Inc. 2006:157-191.

Kerbel RS. Tumor Angiogenesis. *N Engl J Med*. 2008;358:2039-2049.

Kerbel RS, Kamen BA. The anti-angiogenic basis of metronomic chemotherapy. *Nat Rev Cancer*. 2004;4:423-436.

National Cancer Institute. Angiogenesis Inhibitors in Cancer Research. Accessed March 3, 2009 at: www.cancer.gov/newscenter/angio.

National Cancer Institute. Angiogenesis Inhibitors Therapy. Accessed March 3, 2009 at: www.cancer.gov/cancertopics/factsheet/therapy/angiogenesis-inhibitors.

Scappaticci, FA. Mechanism and future directions for antiangiogenesis-based cancer therapies. *J Clin Oncol*. 2002;20:3906-3927.

Siemann DW, Chaplin DJ, Horsman MR. Vascular-targeting therapies for treatment of malignant disease. *Cancer*. 2004;100:241-249.

Last Medical Review: 3/10/2009

Last Revised: 3/10/2009