NIH NATIONAL CANCER INSTITUTE

Angiogenesis Inhibitors

What is angiogenesis?

Angiogenesis is the formation of new blood vessels. This process involves the migration, growth, and differentiation of endothelial cells, which line the inside wall of blood vessels.

The process of angiogenesis is controlled by chemical signals in the body. These signals can stimulate both the repair of damaged blood vessels and the formation of new blood vessels. Other chemical signals, called angiogenesis inhibitors, interfere with blood vessel formation. Normally, the stimulating and inhibiting effects of these chemical signals are balanced so that blood vessels form only when and where they are needed.

Why is angiogenesis important in cancer?

Angiogenesis plays a critical role in the growth and spread of cancer. A blood supply is necessary for tumors to grow beyond a few millimeters in size. Tumors can cause this blood supply to form by giving off chemical signals that stimulate angiogenesis. Tumors can also stimulate nearby normal cells to produce angiogenesis signaling molecules. The resulting new blood vessels "feed" growing tumors with oxygen and nutrients, allowing the cancer cells to invade nearby tissue, to move throughout the body, and to form new colonies of cancer cells, called metastases.

Because tumors cannot grow beyond a certain size or spread without a blood supply, scientists are trying to find ways to block tumor angiogenesis. They are studying natural and synthetic angiogenesis inhibitors, also called antiangiogenic agents, with the idea that these molecules will prevent or slow the growth of cancer.

How do angiogenesis inhibitors work?

Angiogenesis requires the binding of signaling molecules, such as vascular endothelial growth factor (VEGF), to receptors on the surface of normal endothelial cells. When VEGF and other endothelial growth factors bind to their receptors on endothelial cells, signals within these cells are initiated that promote the growth and survival of new blood vessels.

Angiogenesis inhibitors interfere with various steps in this process. For example, bevacizumab (Avastin®) is a monoclonal antibody that specifically recognizes and binds to VEGF (1). When VEGF is attached to bevacizumab, it is unable to activate the VEGF receptor. Other angiogenesis inhibitors, including sorafenib and sunitinib, bind to receptors on the surface of endothelial cells or to other proteins in the downstream signaling pathways, blocking their activities (2).

Are any angiogenesis inhibitors currently being used to treat cancer in humans?

Yes. The U.S. Food and Drug Administration (FDA) has approved bevacizumab to be used alone for glioblastoma that has not improved with other treatments and to be used in combination with other drugs to treat metastatic colorectal cancer, some non-small cell lung cancers, and metastatic renal cell cancer. Bevacizumab was the first angiogenesis inhibitor that was shown to slow tumor growth and, more important, to extend the lives of patients with some cancers.

The FDA has approved other drugs that have antiangiogenic activity, including sorafenib (Nexavar®), sunitinib (Sutent®), pazopanib (Votrient®), and everolimus (Afinitor®). Sorafenib is approved for hepatocellular carcinoma and kidney cancer, sunitinib and everolimus for both kidney cancer and neuroendocrine tumors, and pazopanib for kidney cancer. Researchers are exploring the use of angiogenesis inhibitors to treat other types of cancer. In addition, angiogenesis inhibitors are being used to treat some diseases that involve the development of abnormal blood vessel growth in noncancer conditions, such as macular degeneration.

How are angiogenesis inhibitors different from conventional anticancer drugs?

Angiogenesis inhibitors are unique cancer-fighting agents because they tend to inhibit the growth of blood vessels rather than tumor cells. In some cancers, angiogenesis inhibitors are most effective when combined with additional therapies, especially chemotherapy. It has been hypothesized that these drugs help normalize the blood vessels that supply the tumor, facilitating the delivery of other anticancer agents, but this possibility is still being investigated.

Angiogenesis inhibitor therapy does not necessarily kill tumors but instead may prevent tumors from growing. Therefore, this type of therapy may need to be administered over a long period.

Do angiogenesis inhibitors have side effects?

Initially, it was thought that angiogenesis inhibitors would have mild side effects, but more recent studies have revealed the potential for complications that reflect the importance of angiogenesis in many normal body processes, such as wound healing, heart and kidney function, fetal development, and reproduction. Side effects of treatment with angiogenesis inhibitors can include problems with bleeding, clots in the arteries (with resultant stroke or heart attack), hypertension, and protein in the urine (3–5). Gastrointestinal perforation and fistulas also appear to be rare side effects of some angiogenesis inhibitors. Animal studies have revealed the potential for birth defects, although there is no clinical evidence for such effects in humans.

It is likely that some of the possible complications of angiogenesis inhibitor therapy remain unknown. As more patients are treated with these agents, doctors will learn more about possible rare side effects.

What is the ongoing research on angiogenesis inhibitors?

In addition to the angiogenesis inhibitors that have already been approved by the FDA, others that target VEGF or other angiogenesis pathways are currently being tested in clinical trials (research studies involving patients). If these angiogenesis inhibitors prove to be both safe and effective in treating human cancer, they may be approved by the FDA and made available for widespread use.

In addition, phase I and II clinical trials are testing the possibility of combining angiogenesis inhibitor therapy with other treatments that target blood vessels, such as tumor-vascular disrupting agents, which damage existing tumor blood vessels (6).

The list below includes cancers that are being studied in active phase III treatment clinical trials using angiogenesis inhibitors. The clinical trials can be found in NCI's list of clinical trials. For information about how to search the list, see Help Finding NCI-Supported Clinical Trials.

Types of Cancer in Active Phase III Treatment Clinical Trials of Angiogenesis Inhibitors:

- Breast cancer

- Colorectal cancer
- Esophageal cancer
- Gastrointestinal stromal tumor (GIST)
- Kidney (renal cell) cancer
- Liver (adult primary) cancer
- Lymphoma
- Melanoma
- Non-small cell lung cancer (NSCLC)
- Ovarian epithelial cancer
- Pancreatic cancer
- Prostate cancer
- Stomach (gastric) cancer

For more information about NCI's clinical trials database and other cancer-related information, call NCI's Cancer Information Service at 1–800–4–CANCER (1–800–422–6237).

Selected References

1. Shih T, Lindley C. Bevacizumab: an angiogenesis inhibitor for the treatment of solid malignancies. *Clinical Therapeutics* 2006; 28(11):1779–1802. [PubMed Abstract]
2. Gotink KJ, Verheul HM. Anti-angiogenic tyrosine kinase inhibitors: what is their mechanism of action? *Angiogenesis* 2010; 13(1):1–14. [PubMed Abstract]
3. Cook KM, Figg WD. Angiogenesis inhibitors: current strategies and future prospects. *CA: A Cancer Journal for Clinicians* 2010; 60(4):222–243. [PubMed Abstract]
4. Chen HX, Cleck JN. Adverse effects of anticancer agents that target the VEGF pathway. *Nature Reviews Clinical Oncology* 2009; 6(8):465–477. [PubMed Abstract]
5. Verheul HM, Pinedo HM. Possible molecular mechanisms involved in the toxicity of angiogenesis inhibition. *Nature Reviews Cancer* 2007; 7(6):475–485. [PubMed Abstract]
6. Siemann DW. The unique characteristics of tumor vasculature and preclinical evidence for its selective disruption by Tumor-Vascular Disrupting Agents. *Cancer Treatment Reviews* 2011; 37(1):63–74. [PubMed Abstract]

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