Endostatin: Are We Waiting For Godot?

After trials of the angiogenesis inhibitor endostatin ended, Judah Folkman, M.D., of the Children’s Hospital Boston and Harvard Medical School was dismayed. “There are four patients who have been on endostatin for 3.5 years or more with metastases of the liver. The tumors have stopped growing or arrested, mainly arrested. [The patients] love the drug. They don’t lose their hair, they [maintain] normal weight, they’re not nauseated, they go back to work, and they have strength.”

But the clinical studies of endostatin stopped in February 2005, and supplies ran out a few months later. “After August 2, 2005, there was no more [endostatin] in the United States,” said Folkman, whose laboratory discovered the molecule about a decade ago.

Endostatin is a protein produced by a fragment of the human gene collagen XVIII. Research by Folkman and others showed it could be a potent inhibitor of angiogenesis, a process that triggers blood vessel formation in so they grow larger. Following a New York Times feature, the drug was rapidly pushed to clinical trials.

By traditional measures, early trials of endostatin failed. But angiogenesis inhibitors don’t affect tumors the same way chemotherapy drugs do, raising questions of whether scientists should use the same measure of “response” used for standard chemotherapy. Also, scientists disagree about what biological mechanisms endostatin uses. Researchers suggest if they knew more about the biological pathways endostatin effects, a clinical trial could be designed to evaluate its ability to inhibit tumor angiogenesis.

A newly developed compound called Endostar, a variation of endostatin, has moved the drug back into the spotlight, but a lack of peer-reviewed, published data raises questions about whether researchers should jump to investigate this new compound or move on to other angiogenesis inhibitors that could be more promising.

Clinical Trials

Initial laboratory tests of endostatin were positive; the protein blocked tumor growth and decreased the incidence of lesions in rats with breast carcinomas. Other studies suggested it blocked tumor growth and increased tumor cell death. The drug itself contains the endostatin protein, and a dose increases levels of the protein in the body. A company called EntreMed began to manufacture endostatin in 1996, and Folkman’s lab started a phase I trial in 1999 to study its effects in human cancer patients. The trials included patients with breast, lung, liver, pancreas, ovary, colorectal, and kidney cancers, as well as fibrosarcoma and melanoma. The phase I trial showed the drug was safe and had no toxic effects. But according to J. Paul Eder, M.D., of the Dana-Farber Cancer Institute in Boston, the drug showed little or no clinical effect on the progression of cancer in the trials or in surrogate tests of antiangiogenic activity. Phase II trials began in 2002 for melanoma and neuroendocrine tumors. Once dose levels were increased from minimal doses up to 90 or 120 mg, Folkman said some tumors stabilized or shrank at a slow rate.

Eder agrees there was a small effect at the higher doses, “The phase II trials showed a number of patients who were stable. Tumors didn’t get worse, some had minor shrinkage. When the sponsor stopped making the compound, there were still four patients out of 40 or so who were still stable.”

EntreMed eventually ran into production problems. The company couldn’t handle the high volume of endostatin needed for trials to continue, and its production was expensive. Meanwhile, the drug wasn’t advancing to phase III trials because phase II studies mostly showed no tumor response. EntreMed stopped making the drug in February 2004 and transferred rights to the Children’s Hospital Boston and a company called Alchemgen Therapeutics Inc., which wanted to manufacture it in Asia. Supplies of
endostatin ran out in August 2005, and Folkman’s patients had to stop therapy.

According to Folkman, the trials didn’t fail. He said the problem lies in the nomenclature used to evaluate whether antitumor drugs are effective. “Using chemotherapy nomenclature, if a cytotoxic agent treats the tumor 100%, it’s called complete response,” Folkman said. “If it shrinks [the tumor] 50%, it’s called partial response. Less tumor shrinkage is called no response.”

However, angiogenesis inhibitors work more slowly than traditional cytotoxic chemotherapy drugs, scientists explained, and they often cause little or no toxic effects, making it difficult to establish a maximum tolerated dose. These drugs may shrink tumors, but they often just stop their growth because, instead of targeting the cancer cells as cytotoxic drugs do, angiogenesis inhibitors target the blood vessels that help tumors grow. (See News, Vol. 95, No. 19, p. 1425, “Evidence of Efficacy: Researchers Investigating Markers for Angiogenesis Inhibitors.”)

“But if a patient’s tumor regresses 10% a year, or remains stable with no side effects, this is called ‘no response’ and is considered a drug failure. The nomenclature has to be changed,” Folkman said.

Robert Kerbel, Ph.D., of Sunnybrook Health Sciences Center in Toronto, agreed that the traditional nomenclature is outdated. “I think most of us in the field feel that the traditional criteria that are used to evaluate cytotoxic chemotherapy drugs, such as response rates based on tumor shrinkage, are not appropriate for a number of the new targeted therapies, not just antiangiogenic drugs.” Kerbel suggested that new drugs may work to prolong survival or stabilize disease rather than reducing or eliminating tumor cells, which is more difficult to evaluate in a clinical trial.

“I think that there is growing skepticism about the use of response rate data even with respect to traditional cytotoxic chemotherapy because there are growing numbers of examples where response rate data simply do not necessarily provide an indication of subsequent survival activity in terms of prolonging overall survival.”

**Defining the Mechanism**

Compared with FDA-approved angiogenesis inhibitors like bevacizumab (Avastin), researchers don’t know the biological mechanisms of endostatin. Endostatin doesn’t seem to affect a small number of molecular pathways or genes but instead it affects a wide variety of targets. Two papers published in 2004 and 2005 by Amir Abdollahi, M.D., of the University of Heidelberg Medical School in Germany, and colleagues examined endostatin’s activity by using microarrays. The results suggested that around 12% of all genes in cells exposed to endostatin are affected. Specifically, endostatin appeared to act on genes that increased levels of known angiogenesis inhibitors and decreased levels of molecules that stimulated angiogenesis.

Known targets of endostatin include α5β1 integrin, a molecule on the lining of body cavities and blood vessels; E-selectin, a molecule on the surface of epithelial cells involved in the inflammatory response; and several metalloproteinases, enzymes that bind metallic ions and are active in tumor metastasis. But endostatin’s mechanism can’t be reduced to a few simple pathways. In comparison, bevacizumab has a molecular target that acts on a known pathway: It neutralizes one molecule known to promote angiogenesis, called vascular endothelial growth factor A (VEGF-A).

But because researchers don’t know exactly how endostatin works in the body, it’s difficult to ascertain how to administer the drug clinically. Folkman said patients need continuous levels of endostatin in the blood to prevent angiogenesis and keep tumors from growing. A paper published in 2005 in the Proceedings of the National Academy of Sciences by Raghu Kalluri, Ph.D., of Beth Israel Deaconess Medical Center and Harvard Medical School in Boston, and colleagues indicated that a consistent 160% increase in levels of endostatin reduces tumor growth by 300%.

“I think clearly there is something there,” said Giovanna Tosato, M.D., of the National Cancer Institute in Bethesda, Md. “There have been clinical observations that are pointing to a role for these molecules. It just seems that perhaps a lot of the more basic work needs to be done to characterize what these molecules are and the way they work. We need more information.”

Tosato said more basic science information could have helped scientists assess endostatin’s action in clinical trials. “It’s very difficult to even assess how effective or powerful [endogenous angiogenesis inhibitors] are or what their biological activity is because it is difficult to have stringent criteria for evaluating whether the protein is active,” she said.

Such information could help in trial design. “Unless we know how endogenous angiogenesis inhibitors work in the body, we can’t design our trials in an intelligent way to assess the activity,” Kalluri said. “Otherwise, it’s an inhibitor without known mechanism that you put in and don’t know what the readout should be or what it should target. Endostatin may have gone into clinical trials a little bit early before anyone knew how it really worked.”

**A Future in Endostar?**

After results of the phase II trials were published, a group of Chinese scientists, including one of the original investors in EntreMed, Luo Yongzhang, Ph.D., of Tsinghua University in Beijing, decided to alter endostatin and give the drug a new trial in Chinese patients. They named it Endostar, meaning “gracious.”

Folkman said Chinese scientists made a few amino acid alterations that made Endostar soluble, and they made it so patients could take it every other day instead of daily. “It lasts a lot longer in the blood,” he said. “That’s a big improvement.” According to results reported at a medical conference in May 2005, patients taking Endostar—like those on endostatin—have experienced no side effects.

Chinese scientists used Endostar in combination with traditional chemotherapeutic agents, which Kerbel suggests could be a reason that reports say that the drug showed a survival benefit in phase III Chinese trials. He said a combination with chemotherapeutic agents may be a key to the success
of angiogenesis inhibitors like endostatin or bevacizumab. “Antiangiogenic drugs such as Avastin seem to work best, or only, when they are combined with another therapy, which so far is standard chemotherapy.”

Results of Chinese trials on Endostar haven’t yet been published in peer-reviewed journals.

“There’s no published information as to what exact changes were made to the endostatin backbone to make Endostar,” Kalluri said. “For the moment, we know that something like this exists, but as a scientist I need to see the actual published data.”

For Folkman, new research on Endostar could mean that patients currently unable to obtain endostatin could regain access to a life-saving therapy. For others, trials on endostatin or Endostar should be postponed indefinitely until scientists have more clearly defined how endostatin acts in the body or even until more promising therapies emerge.

“Right now, I think endostatin has a huge hurdle to overcome, unlike 7 or 8 years ago when there really was no other competition,” Eder said. “At that time, even though endostatin was hard to make and hard to administer, people said, ‘This is a whole new breakthrough.’ Now we can say, ‘We have drugs that can target angiogenesis a lot easier and a lot simpler.’”

Tosato is in favor of waiting until more knowledge about how endostatin works is uncovered. But she acknowledges that medicine hasn’t always relied on a cautious approach. “If people wanted to know how penicillin worked, we would have waited for a very long time,” Tosato said. “Penicillin saved many lives before we knew clearly how it worked. There are different ways to look at this issue.”

— Ariel Whitworth