Antiangiogenic Agents: Changing the Nature of Cancer Treatment

by Kate O’Súilleabháin

Magnified 40 times, tiny blood vessels spread across the surface of a mouse mammary tumor like vines claiming a stone wall. These microvessels, which feed tumor growth and metastasis, are also fueling the hopes of researchers engaged in the complex work of developing antiangiogenic therapies.

For decades, many cancer specialists doubted that blood vessels had anything to do with tumor progression. However, in recently recognizing the pioneering work of such researchers as Dr. Judah Folkman (Children’s Hospital/Harvard Medical School), the field has acknowledged that pathologic angiogenesis—the process by which a tumor induces the formation of new blood vessels—holds a vital key to halting cancer.

In preclinical trials, antiangiogenic agents have produced tumor stasis or regression in every type of cancer tested. Even at considerable doses, these drugs do not seem to induce toxicity, a frustrating roadblock in developing chemotherapeutic drugs. By targeting the natural physiologic process responsible for tumor growth, antiangiogenic agents can shut down the mechanisms of cancer progression at an early stage. In short, these drugs offer a logical, nontoxic, and preventive approach to treatment.

“IT’s an exciting time,” said Roy Herbst, M.D., Ph.D., an assistant professor in the Department of Thoracic/Head and Neck Medical Oncology and principal investigator of the multicenter phase I trial of endostatin. “We are trying to treat our patients with the newest and most active agents, and it makes a great deal of sense to target the tumor’s blood supply,” he said.

That is because cells cannot survive or divide more than 150 μm away from a blood vessel.

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Angiogenesis
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as was recently proved in the Department of Cancer Biology at M.D. Anderson. “Any time a tumor expands, take it for granted that what expands first are the blood vessels,” said Isaiah J. Fidler, D.V.M., Ph.D., professor and chairman of the Department of Cancer Biology. By inhibiting neovascularization, antiangiogenic agents cut off the source of blood-borne oxygen and nutrients that fuel tumor growth.

In the phase I trial, treatment with endostatin has resulted in disease stasis in some patients. However, many angiogenesis inhibitors are effective primarily when the tumor is renewing its blood vessels, a process that can take many months. In fact, the introduction of an angiogenesis inhibitor can upset the delicate balance of molecules that controls blood vessel formation and in turn can actually cause tumor growth.

“The tumor’s response to the initiation of an antiangiogenic agent is probably to try to compensate by increasing its production of a stimulator,” said Michael O’Reilly, M.D., assistant professor in the Department of Radiation Oncology at M.D. Anderson, who first isolated endostatin as a researcher in Dr. Folkman’s laboratory.

Although continued use of the therapy can eventually overcome the setback, the treatment protocols of most clinical trials last only three months, which may not be enough time for antiangiogenic drugs to produce their full effect. And because chemotherapy agents target endothelial cells, albeit indirectly, previous treatment raises the threshold of resistance to antiangiogenic agents, further increasing the time to response and frustrating attempts to show short-term results in the clinical setting. In future proposals for clinical studies, researchers will seek approval for longer trials of this unique class of drugs.

“Investigators have to design a whole new standard of surrogate markers and a whole new standard for response to evaluate these new drugs,” Dr. O’Reilly said.

To assess drug efficacy and to optimize methods of administration, Dr. Fidler and his laboratory research team are identifying surrogate markers—molecules that indicate the level of disease activity.

“We can measure the shorter-term efficacy of a given drug by measuring the level of its targeted biologic marker rather than the tumor size,” Dr. Fidler said. In a trial of interferon-alpha in mice, Dr. Fidler’s team measured levels of basic fibroblast growth factor, matrix metalloproteinase-9, interleukin-8, and vascular endothelial growth factor. The marker levels indicated that low doses of interferon delivered daily via subcutaneous injection were more effective in fending off disease than were high doses of interferon delivered two or three times weekly.

In addition to analyzing biopsy specimens and measuring levels of growth factors in blood plasma or urine, researchers are using nuclear imaging to measure the short-term effects of antiangiogenic agents on tumors. David Yang, Ph.D., associate professor in the Department of Nuclear Medicine, uses positron emission tomography and single-photon emission computed tomography to measure the degree of radiisotope absorbance, a parameter that can predict whether tumors will metastasize. Such information is important in choosing therapy, since patients with metastatic tumors are unlikely to benefit from surgery. Researchers anticipate that the next decade will witness the development of highly specialized molecular imaging techniques that identify specific drug targets in individual tumors.

The nontoxic nature of antiangiogenic compounds makes it difficult to identify the most effective dosing regimens, thus posing another challenge to appropriately designing clinical trials. In the laboratory, antiangiogenic drugs

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PROTOCOLS

Clinical Trials of Antiangiogenic Agents

Clinical trials at The University of Texas M. D. Anderson Cancer Center include the following studies of antiangiogenic agents in patients with solid tumors.

- A phase I/II trial of SU5416 in patients with recurrent high-grade astrocytomas or mixed gliomas (NABTC99-02). *Physician: W.K. Alfred Yung, M.D.*
- A phase II study to evaluate the efficacy of recombinant interferon-alpha in the treatment of patients with recurrent unresectable meningioma and malignant meningioma (ID96-296). *Physician: W.K. Alfred Yung, M.D.*
- Phase II study of thalidomide for patients with progressive metastatic renal cell carcinoma following treatment with interleukin-2 (ID99-314). *Physician: Danai Dallani, M.D.*
- A phase I study of a continuous infusion of TNP-470 alone or with a combination of paclitaxel and carboplatin in adult patients with solid tumors (ID99-267). *Physician: Roy Herbst, M.D., Ph.D.*
- A phase I/II study of conformal radiation therapy plus interferon alfa-2b and cis-retinoic acid for newly diagnosed supratentorial glioblastoma (ID01-005). *Physician: Mark R. Gilbert, M.D.*
- Phase II study of anti–epidermal growth factor receptor (EGFR) antibody C225 in combination with chemotherapy in patients with metastatic or recurrent squamous cell head and neck carcinoma (ID99-164). *Physician: Roy Herbst, M.D., Ph.D.*
- Phase II study of SU5416 for patients with progressive metastatic renal...
at maximum tolerated doses are ineffective in combating cancer. In a preclinical study of interferon, Dr. Fidler found that the optimal biologic dose—the drug level at which the surrogate markers of disease were lowest—was only one tenth the maximum tolerated dose. “As you increase the dose toward tolerance, the markers become elevated because the cells no longer respond to interferon,” he said.

In fact, the cells reach a state of tolerance that destroys the very signaling cascade on which the efficacy of these drugs depends. Because the relationship between dosage and efficacy is nonlinear and because these agents are, at least in the short term, nontoxic, future trials should attempt to identify the optimal biologic doses rather than the maximum tolerated doses.

Most antiangiogenic agents are still in the early stages of clinical assessment, but the results so far suggest that these drugs cause disease stabilization, rather than regression, in humans. A reduction in the time to disease progression has been an important finding, since it proves that the drugs render tumor cells incapable of growth. Nevertheless, it is somewhat disappointing that patients did not show the marked tumor shrinkage seen earlier in laboratory mice.

“We have to lower our goals in cancer treatment,” said Lee Ellis, M.D., an associate professor in the Department of Surgical Oncology. “We need to slow growth of tumors to a point where patients can live with their disease as a chronic condition.”

By slowing or stopping tumor growth and metastasis, angiogenesis inhibitors could provide the first “maintenance therapy” for solid tumors. Angiogenesis inhibitors might also prove effective in preventing disease in patients at high risk for various malignancies. In addition, they might be useful in early-stage cancers to prevent disease recurrence among patients who have undergone surgical resection of the primary tumor. Eventually, clinicians hope to combine antiangiogenic agents with chemotherapy to stave off tumor progression. Researchers have also begun to explore the synergy between antiangiogenic agents in the laboratory. When administered to mice, the combination of (Continued on page 4)
Angiogenesis
(Continued from page 3)

Some Angiogenesis Inhibitors in Clinical Development at M. D. Anderson

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<tr>
<th>Mechanism of Angiogenesis Inhibition*</th>
<th>Specific Action</th>
<th>Description</th>
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<tr>
<td><strong>DRUGS THAT BLOCK MATRIX BREAKDOWN</strong></td>
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<tr>
<td>Marinastat</td>
<td>Inhibitor of all matrix metalloproteinases</td>
<td>Synthetic agent</td>
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<td><strong>AGENTS THAT INHIBIT ENDOTHELIAL CELLS DIRECTLY</strong></td>
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<tr>
<td>Thalidomide</td>
<td>Unknown</td>
<td>Derivative of synthetic glutamic acid</td>
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<tr>
<td>Squalamine</td>
<td>Blocks NHE3, a mediator of sodium and hydrogen exchange</td>
<td>Extract of dogfish liver (now produced synthetically)</td>
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<tr>
<td>Endostatin</td>
<td>Inhibits two antiapoptotic proteins, Bcl-2 and Bcl-x&lt;sub&gt;L&lt;/sub&gt;</td>
<td>Protein isolated from marine hemangioendothelioma cells (recombinant human endostatin is produced in the yeast Pichia pastoris)</td>
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<tr>
<td>TNP-470</td>
<td>Inhibits housekeeping enzyme methionine aminopeptidase-2; causes cell-cycle arrest among cycling endothelial cells</td>
<td>Furamoglobin analogue</td>
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<tr>
<td><strong>AGENTS THAT BLOCK ACTIVATORS OF ANGIOGENESIS</strong></td>
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<td>SU5416</td>
<td>Blocks signaling of VEGF</td>
<td>Tyrosine kinase inhibitor</td>
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<td>SU6668</td>
<td>Blocks signaling of receptors of VEGF, FGF, and PDGF</td>
<td>Tyrosine kinase inhibitor</td>
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<tr>
<td>Interferon-alpha</td>
<td>Activates NK cells; impedes production of bFGF and VEGF</td>
<td>Primary interferon produced by virus-induced laukoyte cultures</td>
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<tr>
<td>C225</td>
<td>Inhibits EGFR; indirectly inhibits angiogenic factor expression</td>
<td>Monoclonal antibody</td>
</tr>
<tr>
<td>Anti-VEGF antibody</td>
<td>Binds and blocks VEGF</td>
<td>Monoclonal antibody</td>
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*Drugs are listed according to categories established by the National Cancer Institute (http://cancer.gov/nci-nets/docs/cancer-alphabet-table.html).
Abreviations: VEGF = vascular endothelial growth factor; FGF = fibroblast growth factor; PDGF = platelet-derived growth factor; NK = natural killer; bFGF = basic fibroblast growth factor; EGFR = epidermal growth factor receptor.

Angiostatin and endostatin is 10 times more efficacious than either drug alone.

Although the results of preclinical trials of antiangiogenic agents are promising, researchers at M. D. Anderson are cautious in their approach to using these drugs in humans. To date, almost everything known about these agents comes from preclinical trials. A growing area of concern is that although these drugs are nontoxic, their long-term use may produce toxicity. For nonregenerating tissues, such as muscle and brain, agents that target endothelial cells could prove damaging.

"I'm very vocal now about the fact that we have to be very selective in our antiangiogenic or anti-vascular approach," Dr. Fidler said. "We cannot afford to damage blood vessels in vital organs, because the cells in these vital organs might be irreplaceable."

Researchers must also continue to identify the mechanisms that underlie pathologic angiogenesis and to develop agents that address all the molecular targets involved.

"Angiogenesis is a complex process, not a simple one, and may be regulated by lots of molecules that substitute for one another," said Dr. Ellis. In addition, most tumors are heterogeneous, with their various components responding at varying rates to different drugs.

The results of the endostatin trial at M. D. Anderson may provide insights into overcoming these complexities. To monitor disease status and response, the investigators are analyzing biopsy specimens and positron emission tomography scans in the hope that this information will guide future trial design.

Dr. O'Reilly said he believes that investigators have designed the endostatin trial, with its comprehensive approach to patient selection and disease assessment, to guide most if not all future trials of these unique agents. "There is still a lot of work to be done, but they have set the standard," he said.

For more information, contact Dr. Herbst at (713) 792-6363, Dr. Fidler at (713) 792-8580, Dr. O’Reilly at (713) 745-0484, or Dr. Ellis at (713) 792-6926.

Recognition Spurs Osteoporosis in Life

The recognition that survivors of certain types of cancer are at increased risk for developing osteoporosis later in life was a turning point in the prevention and treatment of this debilitating disease, said Rena Sellin, M.D., a professor in the Department of Endocrine Neoplasia and Hormonal Disorders at The University of Texas M. D. Anderson Cancer Center.

Likewise, being able to recognize at-risk patients and knowing how to treat them is critical to preventing the crippling effects of osteoporosis in patients with cancer.

"Over the past 10 years, there has been a lot more attention paid to osteoporosis, and a lot more treatment options have become available," said Dr. Sellin, who also directs the Life After Cancer Care Clinic at M. D. Anderson.

Osteoporosis, a disease of reduced bone mass and increased susceptibility to fractures, affects 10 million Americans; 18 million more have osteopenia, the common precursor to osteoporosis. The risk factors for osteoporosis include advanced age, a small frame, a family history of osteoporosis, low testosterone levels in men, being female (more than 80% of cases occur in women), and being postmenopausal. What is it then that makes cancer patients at high risk for the condition?

"There are certain diseases themselves," said Dr. Sellin, "and then there are diseases where the treatment induces osteoporosis."

In several child and adult leukemias and lymphomas, the malignant cells produce certain cytokines that increase osteoclastic bone activity and promote bone loss. However, more often than not, it is the treatment that induces
Patients with Cancer

bone resorption. For instance, long-term use of such glucocorticoids as prednisone and cortisone, which are often used to treat patients with leukemias and lymphomas, can cause even further bone loss.

Steroids, along with cranial irradiation, can also cause growth hormone deficiencies. According to Dr. Sellin, most bone development occurs by the age of 25, so once many survivors of childhood cancers reach adulthood, they are at increased risk for osteoporosis, not because their bones have deteriorated but because they have not accumulated normal bone masses.

Another group of at-risk patients are those treated for hormone-responsive cancers. Prostate cancer, for example, is commonly treated with orchietomy (excision of one or both of the testes) or with the antineoplastic agent leuprolide (Lupron), both of which cause androgen ablation or deficiency. Similarly, women with breast cancer who develop early menopause are at increased risk of developing osteoporosis. According to the National Osteoporosis Foundation (NOF), women often lose up to 20% of their bone mass in the five to seven years after menopause, and for some women with breast cancer, this loss of bone mass can begin up to 10 years earlier than normal. Furthermore, chemotherapy and radiation therapy (not necessarily associated with breast and prostate cancers) can cause gonadal damage, which may also cause a loss of estrogen or testosterone.

"Since estrogen or testosterone deficiency leads to bone loss," said Dr. Sellin, "prompt and careful replacement is important for these patients."

Hormone-replacement therapy with estrogen, estradiol and progestin, or testosterone can be used to prevent and treat osteoporosis in many of these individuals, although estrogen-replacement therapy is contraindicated in patients with breast cancer. For those patients, other drugs are available, such as raloxifene (Evista), a selective estrogen receptor modulator approved by the Food and Drug Administration (FDA) to both prevent and treat osteoporosis. Similarly, tamoxifen, which is often used as adjuvant therapy after breast cancer, has also been found to protect against bone loss in postmenopausal women.

Another FDA-approved drug for preventing and treating osteoporosis is alendronate (Fosamax), a bisphosphonate, or agent that inhibits bone resorption at sites of osteoid mineralization. According to the NOF, this drug is often indicated specifically for the treatment of steroid-induced osteoporosis. Calcitonin (Miacalcin), a naturally occurring hormone that is important for calcium regulation and bone metabolism, has also been approved in the form of a nasal spray to treat osteoporosis.

"Since estrogen or testosterone deficiency leads to bone loss, prompt and careful replacement is important."

- Rena Sellin, M.D., professor, Department of Endocrine Neoplasia and Hormonal Disorders

mainly in postmenopausal women.

According to Dr. Sellin, all of these agents work by inhibiting the activity of osteoclasts. While many of them have also been shown to increase bone density, they work primarily by inhibiting bone resorption so that normal bone formation can occur more quickly.

"For the most part, agents that are used in patients with cancer to treat osteoporosis are similar to the agents that are used in other patients," said Dr. Sellin. The biggest difference is that patients with cancer have certain contraindications that limit the number of drugs they can choose from.

Aside from medications, a healthy lifestyle can be the biggest key to preventing osteoporosis and the hip, spine, and wrist fractures commonly associated with reduced bone mass. Quitting smoking, increasing calcium intake, limiting alcohol consumption, treating metabolic and endocrine disorders, and exercising can all contribute. While weight-bearing exercises have been shown to improve muscle mass (which protects bones), in many instances they also result in fractures in individuals whose bones are already weak. According to Dr. Sellin, a healthy alternative is to exercise in the water.

"Exercising in water allows patients who have feeble skeletons to stretch and increase muscle tone and muscle mass without putting their bones at risk," Dr. Sellin said.

Beyond that, Dr. Sellin advises patients to use common sense in their daily activities, including wearing shoes with nonslip soles and abstaining from activities that could increase the risk of falling.

For more information, contact Dr. Sellin at (713) 792-2841.
We Want to Hear from You

Your opinions are important to us. Please take a few moments to complete the survey below, and return it to OncoLog Survey, Department of Scientific Publications–Box 234, M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030. Or simply fax your answers to (713) 794-1370. Your responses will help us ensure that OncoLog continues to meet your cancer information needs. Thank you!

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4. I photocopy House Call (patient education page) articles and distribute them to my patients. ○ Yes ○ No
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II. Please indicate the overall quality (e.g., importance, usefulness, and appeal) of the following OncoLog regular features.

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<td>House Call (patient education page)</td>
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<td>DialLog (editorial on back page)</td>
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<td>Protocols</td>
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<td>Compass (quarterly insert of treatment guidelines)</td>
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III. Indicate your level of interest in the following topics.

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IV. Please answer the following questions.

1. How long have you been receiving OncoLog?

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2. After reading OncoLog, I (circle one):
   a. Save it for future reference
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Age______________

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Specialty______________

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Location of practice (circle one):
   Rural Urban Suburban Other

Type of practice (circle one):
   Group Solo Institution Other

VI. Personal information (optional):

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6 / OncoLog
The cancer treatment is finally over. Now the waiting begins. Is that bad cough or muscle cramp a sign that cancer has returned? Do all former patients feel so anxious every time they have a checkup?

Yes, it's normal for cancer survivors to fear a reappearance of their disease. Cancer may recur at any time from a few weeks to many years after treatment ends. Originating from cancer cells that were not destroyed or removed by the original therapy, the recurring cancer may affect an entirely different part of the body. Colon cancer, for example, might spread to the liver, but the disease is still colon cancer.

So what can patients with cancer do to help themselves better deal with this legitimate concern? Here are a few tips from the National Cancer Institute's Facing Forward: A Guide for Cancer Survivors.

**Get regular checkups from a physician specializing in cancer care.**

Most people who have been treated for cancer return to their doctor for follow-up visits every three to four months at first and once or twice a year later on. Long-term cancer survivors need a yearly physical.

**Learn the signs of a possible return of cancer and the late effects of treatment.**

Ask your physician which symptoms to look for and what you should do if they occur. Remember also that most aches and pains are not indications that your cancer has come back.

**Give your doctors the information they need to prescribe the best care.**

See that all your physicians receive a copy of your cancer medical records.

**Tell them about any symptoms you are having, any changes in your lifestyle such as stopping smoking, or any fears or concerns you have about your health.**

With early detection, cancers such as breast, prostate, and colon cancers often can be controlled.

**Maintain good health habits.**

Eat right, get enough sleep, stop smoking, and exercise regularly, if you can. This will help you feel better.

**Discuss your feelings with others.**

Talk with family and friends, letting them know what they can do to help you. A social worker who specializes in working with patients with cancer can help you handle your concerns as well as arrange for practical assistance with home care, dealing with health and social service systems, financial planning, or child care. Talking with a mental health professional—a psychologist, psychiatrist, clinical social worker, or nurse therapist—is valuable for many people.

**Consider joining a cancer survivors' group.**

Such support groups can help participants feel better about themselves, improve their moods, have better pain control, and make new friends. If you don't care to join a group, you may want to call a cancer telephone hotline to ask the hotline to introduce you to another cancer survivor similar to you. The two of you can give each other emotional support and advice over the phone.

**Help others.**

It will make you feel stronger and more in control.

**Be good to yourself.**

Do activities you enjoy and try to eliminate ones you don't. Think kindly about yourself, looking for the positive. Learn how to set priorities and how to say no. Rest before you are tired. Take things one day at a time.

**Finally, remind yourself that there is hope.**

More than 8 million people in America have survived cancer for at least five years—and that number is increasing every single day.

For more information, contact your physician or contact the M. D. Anderson Information Line:

- (800) 392-1611 within the United States, or
- (713) 792-6161 in Houston and outside the United States.

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Angiogenesis Research: Looking for New Ways to Measure Success

Roy S. Herbst, M.D., Ph.D.
Assistant Professor, Department of Thoracic/Head and Neck Medical Oncology

Despite many advances in their treatment, cancers of the lung, colon, breast, and pancreas claim 350,000 lives every year, and most of these patients die from metastatic disease. Clearly, we need better therapies for these cancers—agents that work against specific molecular targets.

One such target is angiogenesis, the formation of new blood vessels by tumor cells. There are at least 20 angiogenesis inhibitors in clinical testing. At M. D. Anderson, 10 to 15 of these agents are under study, all with different mechanisms of action and all slightly different in scope.

Because they target endothelial cells, which in adults typically do not divide, antiangiogenic agents are enormously specific in most cases, but their effect on tumors is indirect. Instead of causing the tumor to shrink, the agents prevent it from growing by taking away its blood supply.

Ironically, these inhibitors' lack of toxicity can be a problem. For antiangiogenic agents, which might not be toxic at any dose, finding the maximum tolerated dose is impractical. Instead, in the absence of absolute response and toxicity, we try to establish the optimal biologic dose, the level at which the agent has the maximum biologic effect on the tumor. When targeting a specific receptor, more is not necessarily better.

In our trial of human endostatin, I and co-principal investigator James Abbruzzese, M.D., are using three surrogate markers to measure the drug's effect on endothelial cells. First, we are measuring blood flow through the tumor vessels before, during, and after treatment using positron emission tomography with O_15-labeled water. Next, we are examining tissue biopsy specimens for indications of increased endothelial cell death and any changes in blood vessel density. In the third analysis, we are measuring serum markers presumably from the tumor, including serum levels of vascular endothelial growth factor and basic fibroblast growth factor.

Like almost all phase I studies of new drugs, our trial of endostatin is being conducted in patients with advanced disease. In this setting, we don't believe that endostatin and most other antiangiogenesis agents will be that effective alone, although we always remain hopeful. Instead, they will most likely need to be combined with chemotherapy, beginning with preclinical studies. However, in the minimal disease setting, they could be used as single agents or as maintenance therapy—perhaps as chemoprevention in heavy smokers who are at risk for new cancers.

Angiogenesis has promising therapeutic implications, but to discover its full potential, we need new markers, new ways of doing clinical trials, and ultimately, a new way of thinking about cancer therapy.