M. D. Anderson Cancer Center
Is Celebrating Its 60th Anniversary

REPORT TO PHYSICIANS MAY 2001 Vol. 46, No. 5

OncoLog

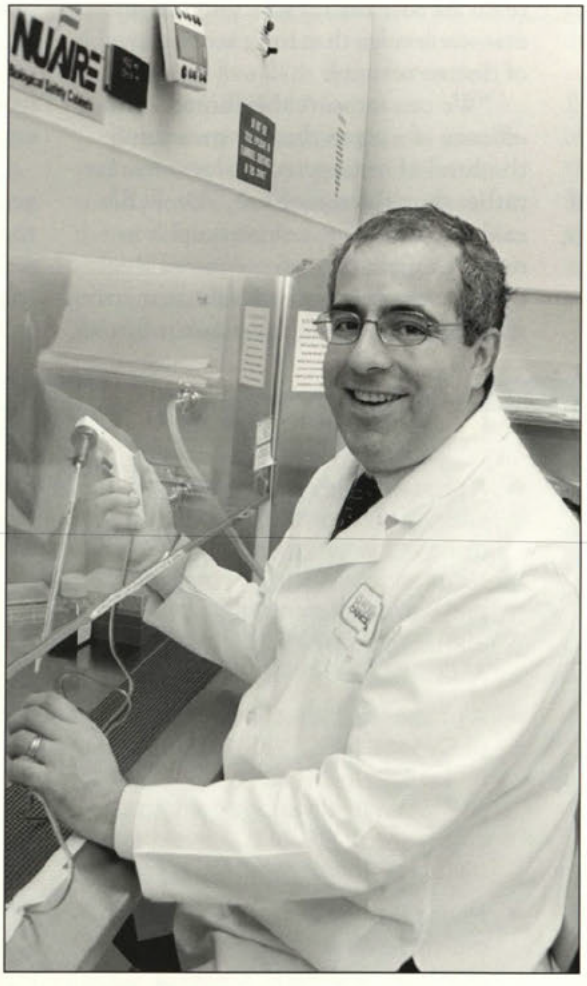
Antiangiogenic Agents: Changing the Nature of Cancer Treatment

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.



Dr. Michael O'Reilly, *an assistant professor in the Department of Radiation Oncology, is studying ways to optimize the combination of angiogenesis inhibitors and radiation therapy or chemotherapy.*

"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,

(*Continued on* **next page**)

THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER

Angiogenesis

(*Continued from* **page 1**)

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., an 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 radioisotope 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

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 surrogate endpoint trial of human recombinant endostatin in patients with advanced solid tumors (ID99-201). *Physician: Roy Herbst, M.D., Ph.D.*
- 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 (DM96-296). *Physician: W.K. Alfred Yung, M.D.*
- A phase I/II study of escalating doses of SU5416 (NSC 696819) in combination with irinotecan (CPT-11) in patients with advanced colorectal carcinoma (ID99-243). *Physician: James L. Abbruzzese, M.D.*
- Phase II study of thalidomide for patients with progressive metastatic renal cell carcinoma following treatment with interleukin-2 (ID99-314). *Physician: Danai Daliani, 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 (DM99-164). *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."

Dr. Roy Herbst, *right, an assistant professor in the Department of Thoracic/Head and Neck Medical Oncology, examines patient* [redacted] *with the help of* **Mercedes Guerra**, *an advanced practice nurse. Dr. Herbst is the principal investigator of several trials of antiangiogenic agents, most notably endostatin.*

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 synergism between antiangiogenic agents in the laboratory. When administered to mice, the combination of

(Continued on **page 4***)*

PROTOCOLS

cancer following treatment with interleukin-2 (ID99-291). *Physician: Christopher J. Logothetis, M.D.*

- Multicenter, open-ended, double-blind, placebo-controlled phase III study of AE-941 in addition to combined-modality treatment (chemotherapy and radiation therapy) for locally advanced unresectable non-small cell lung cancer (ID99-303). *Physician: Charles Lu, M.D.*
- Phase I trial of thalidomide for multiple myeloma (DM98-359). *Physician: Donna M. Weber, M.D.*
- A phase I dose-escalation and pharmacokinetic evaluation of oral LY317615 in patients with advanced cancer (ID00-382). *Physician: Roy Herbst, M.D., Ph.D.*
- A tolerance and efficacy trial of preoperative thalidomide treatment followed by radical retropubic prostatectomy in select patients with locally advanced prostate cancer (ID00-089). *Physician: Danai Daliani, M.D.*
- A phase II trial of thalidomide-dexamethasone for multiple myeloma (ID00-070). *Physician: Donna M. Weber, M.D.*
- Phase II study of gemcitabine-based chemoradiation and TNP-470 for patients with locally advanced, nonmetastatic adenocarcinoma of the pancreas (ID98-248). *Physician: Douglas B. Evans, M.D.*
- Phase I/II study of paclitaxel, estramustine phosphate, and thalidomide for patients with metastatic androgen-independent prostate carcinoma (ID00-087). *Physician: Danai Daliani, M.D.*
- A phase I, single-center, open-label, dose-escalation, safety, and pharmacokinetic study of recombinant human endostatin administered by continuous intravenous infusion to patients with cancer (ID01-074). *Physician: Roy Herbst, M.D., Ph.D.*

FOR MORE INFORMATION *about these clinical trials, physicians or patients may call the M. D. Anderson Information Line. Those within the United States should call (800) 392-1611; those in Houston or outside the United States should call (713) 792-6161. Visit the M. D. Anderson Cancer Center clinical trials Web site at http://www.clinicaltrials.org for a broader listing of treatment research protocols.*

Angiogenesis

(*Continued from* **page 3**)

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

Mechanism of Angiogenesis Inhibition*	Specific Action	Description
DRUGS THAT BLOCK MATRIX BREAKDOWN		
Marimastat	Inhibitor of all matrix metalloproteinases	Synthetic agent
AGENTS THAT INHIBIT ENDOTHELIAL CELLS DIRECTLY		
Thalidomide	Unknown	Derivative of synthetic glutamic acid
Squalamine	Blocks NHE3, a mediator of sodium and hydrogen exchange	Extract of dogfish liver (now produced synthetically)
Endostatin	Inhibits two antiapoptotic proteins, Bcl-2 and Bcl-X_L	Protein isolated from murine hemangioendothelioma cells (recombinant human endostatin is produced in the yeast *Pichia pastoris)*
TNP-470	Inhibits housekeeping enzyme methionine aminopeptidase-2; causes cell-cycle arrest among cycling endothelial cells	Fumagillin analogue
AGENTS THAT BLOCK ACTIVATORS OF ANGIOGENESIS		
SU5416	Blocks signaling of VEGF	Tyrosine kinase inhibitor
SU6668	Blocks signaling of receptors of VEGF, FGF, and PDGF	Tyrosine kinase inhibitor
Interferon-alpha	Activates NK cells; impedes production of bFGF and VEGF	Primary interferon produced by virus-induced leukocyte cultures
C225	Inhibits EGFR; indirectly inhibits angiogenic factor expression	Monoclonal antibody
Anti-VEGF antibody	Binds and blocks VEGF	Monoclonal antibody

**Drugs are listed according to categories established by the National Cancer Institute (http://cancertrials.nci.nih.gov/news/angio/table.html). Abbreviations: 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 antivascular 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 Spu Osteoporosis in

by Kerry L. Wright

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

rs Prevention of Patients with Cancer

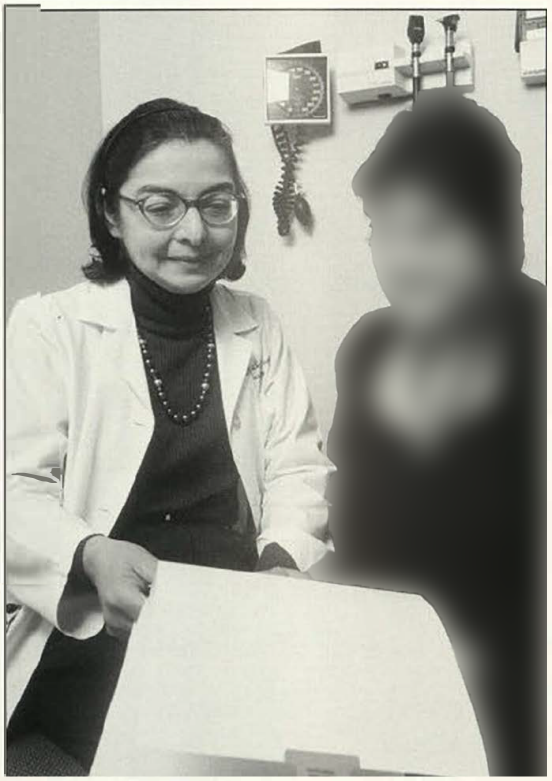
bone resorption. For instance, long-term use of such glucocorticoids as prednisone and cortisone, which are often used to treat patients with leukemias and lymphomas, can cause even further bone loss.

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 orchiectomy (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, estrogen 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.



Dr. Rena Sellin, *left, a professor in the Department of Endocrine Neoplasia and Hormonal Disorders, discusses osteoporosis prevention with a patient in the clinic.*

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, mainly in postmenopausal women.

"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

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!**

I. Please respond Yes or No to the following statements.

1. I read most issues of *OncoLog* that I receive. ❍ Yes ❍ No
2. I read *OncoLog* on the Internet (www3.mdanderson.org/~oncolog). ❍ Yes ❍ No
3. *OncoLog* is useful to me in my practice. ❍ Yes ❍ No
4. I photocopy House Call (patient education page) articles and distribute them to my patients. ❍ Yes ❍ No
5. I have referred a patient to M. D. Anderson. ❍ Yes ❍ No
6. I have referred a patient to M. D. Anderson because of something I read in *OncoLog*. ❍ Yes ❍ No

II. Please indicate the overall quality (e.g., importance, usefulness, and appeal) of the following *OncoLog* regular features.

	Poor	Fair	Good	Excellent
Full-length main articles	1	2	3	4
One-page prevention articles	1	2	3	4
House Call (patient education page)	1	2	3	4
DiaLog (editorial on back page)	1	2	3	4
Protocols	1	2	3	4
Compass (quarterly insert of treatment guidelines)	1	2	3	4

Please comment on any features that you rated especially low or high:

_____

_____

_____

_____

III. Indicate your level of interest in the following topics.

	Not Interested		Neutral	Mildly Interested	Moderately Interested	Strongly Interested	Extremely Interested
Basic cancer research	1	2	3	4	5	6	
Cancer prevention and detection	1	2	3	4	5	6	
Cancer screening guidelines	1	2	3	4	5	6	
Cancer diagnostic guidelines	1	2	3	4	5	6	
Cancer treatment guidelines	1	2	3	4	5	6	
Multidisciplinary care options for patients at M. D. Anderson	1	2	3	4	5	6	
Case reports including workup, staging, and treatment selection	1	2	3	4	5	6	
Social or psychological aspects of patient care	1	2	3	4	5	6	
Ethical issues related to cancer care	1	2	3	4	5	6	
M. D. Anderson departments or programs	1	2	3	4	5	6	

IV. Please answer the following questions.

1. How long have you been receiving *OncoLog*?

_____

2. After reading *OncoLog*, I (circle one):
   a. Save it for future reference
   b. Throw it away
   c. Make it available to colleagues or patients

3. What would you like to see more of in *OncoLog*?

_____

_____

_____

4. What would you like to see less of?

_____

_____

_____

5. Comments about content, writing, or design of *OncoLog:*

_____

_____

_____

_____

V. Demographic information:

Age _____

Sex (circle one) M F

Specialty _____

Years in practice _____

Location of practice (circle one):

Rural Urban Suburban Other

Type of practice (circle one):

Group Solo Institution Other

VI. Personal information (optional):

Name _____

Address _____

_____

_____

Phone _____

E-mail _____

HOUSE•CALL

Overcome Fears of Cancer Recurrence by Taking Action

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.

Get regular screening tests for cancer.

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.*

May 2001

OncoLog

Department of Scientific Publications—234
M. D. Anderson Cancer Center
1515 Holcombe Boulevard
Houston, Texas 77030

www3.mdanderson.org/~oncolog

Address Service Requested

Nonprofit Org.
U.S. Postage
PAID
Permit No. 7052
Houston, TX

DiaLog

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.

Published by the Department of Scientific Publications–234, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030, 713-792-3305.

Made possible in part by a gift from the late Mrs. Harry C. Wiess. Not printed at state expense.