Molecular Therapies Target Bone Metastasis

by Kerry L. Wright

By the time their cancer is diagnosed, more than half of all patients have clinically detectable metastasis or undetected metastatic disease. Yet it takes only one cancer cell—out of the approximately one million cancer cells that circulate each day in the bloodstream and lymphatic system of patients with cancer—to begin the process of metastasis. What is it that guides these cells to seek out a welcoming organ environment, adhere to the organ, and infiltrate it, and how can this process be stopped?

(Continued on next page)

Cell signaling and growth factor expression are two of the mechanisms studied by Dr. Isaiah J. Fidler, chairman of the Department of Cancer Biology, and research assistant Melissa Vanarsdall as molecular therapies that begin in the laboratory are brought to clinical application against bone metastases.
Now, the major problem with cancer is not the primary tumor because surgeons have perfected skills to resect primary tumors, but it is the ability of some cells in a primary tumor to invade distant organs where they give rise to secondary lesions,” said Isaia J. Fidler, Ph.D., D.V.M., professor and chairman of the Department of Cancer Biology at the University of Texas M. D. Anderson Cancer Center.

A kind of complex mating dance occurs between cancer cells and the vascularized environments where metastasis occurs. Tumor cells secrete a unique set of molecular signals that are detected and responded to by only a very few receptive cell types throughout the body. Taking advantage of this, researchers have developed and are now testing several new agents that target molecules to treat, and possibly prevent, metastasis to the bone and other organs by disrupting these signals.

Although cancer can spread to any organ or cell type that has an extensive vasculature, metastases occur most frequently in the brain, lungs, liver, lymph nodes, skin, adrenal glands, and bone. For almost 15 years, researchers like Gabriel Hortobagyi, M.D., chairman and professor in the Department of Breast Medical Oncology, have been developing new treatments specifically for metastasis to the bone, the third most common site of metastatic disease. Often accompanied by intense pain, fractures, and hypercalcemia, bone metastasis frequently originates from primary breast, prostate, and lung cancers, the three most common cancers in the United States, and is in fact the most common site of metastasis in both breast and prostate cancers.

Although metastasis was once thought to be a random process, it is now known to be extremely selective, said Dr. Fidler, who in the 1980s helped prove the long-standing seed and soil hypothesis, which stated that the “seeds,” or cancer cells, can grow only in specific, fertile “soils,” or organ environments.

“In a very simplistic way, we think that cancer cells on the one hand and the endothelium of blood vessels in certain organs on the other hand have what I would call cellular addresses, and when the cellular addresses match, then the malignant cell settles in that organ,” explained Dr. Hortobagyi.

Those cellular addresses, Dr. Hortobagyi said, are actually signaling molecules. For example, many tumor cells express growth factors for specific endothelial cells, and the endothelial cells respond by expressing the corresponding growth factor receptors, starting a cascade within the endothelial cells that leads to the growth of metastatic lesions. Since only endothelial cells that are within the metastasis and up to about 100 µm away from it express the receptors, one approach for treating bone metastasis is to target the vasculature of the lesion by attacking the growth factor receptors, said Dr. Fidler, or by “painting over the address labels,” in Dr. Hortobagyi’s words.

One receptor kinase that is being targeted by this approach is the platelet-derived growth factor receptor (PDGFR), which is specifically expressed in the endothelial cells of metastatic bone lesions. At M. D. Anderson, Paul Mathew, M.D., an assistant professor in the Department of Genitourinary Medical Oncology, is leading a phase I clinical trial of the high-profile drug imatinib mesylate (Gleevec), also known as STI-571 (a small-molecule inhibitor of PDGFR), in combination with the chemotherapeutic drug docetaxel in patients with androgen-independent metastatic prostate cancer. Pathologic markers of apoptosis, proliferation, differentiation, and angiogenesis are being measured in Dr. Fidler’s laboratory to determine any biologic effects of STI-571 on the bone lesions. In addition to PDGFR, epidermal growth factor receptor and vascular endothelial growth factor receptor are potential targets of this type of therapy, said Dr. Fidler.

As are all types of cancer, bone metastases are heterogeneous. They can be lytic, causing destruction (or resorption) of the bone by osteoclasts, or blastic, causing bone growth through increased activity of osteoblasts. While most bone metastases from lung and breast cancers are primarily lytic and most from prostate cancers are blastic, many metastases display both behaviors. Because excessive bone resorption is a fundamental characteristic of both lytic...
and blastic lesions (blastic lesions just have more osteoblastic activity to compensate). Agents that interfere with bone resorption provide another approach for treating bone metastasis.

Bisphosphonates, which have been approved by the U.S. Food and Drug Administration for the management of osteoporosis, are one category of agents that can successfully disrupt bone resorption. Pamidronate, a second-generation bisphosphonate, has also been shown in clinical studies to inhibit osteoclasts and reduce bone resorption by as much as 40% in patients with bone metastases from multiple myeloma and breast cancer, said Dr. Hortobagyi. 

Now, a new generation of bisphosphonates is being studied in large, randomized trials.

Particularly exciting to Dr. Hortobagyi and other bisphosphonate researchers was the approval in January of zoledronic acid, a third-generation bisphosphonate, by the Oncology Drug Advisory Committee of the FDA for the treatment of bone metastasis. Clinical trials of zoledronic acid have shown that it can reduce markers of bone resorption by 40% to 60% in patients with multiple myeloma and breast, prostate, and lung cancers. Zoledronic acid is also being studied for the prevention of bone metastasis in the adjuvant therapy setting, as are the bisphosphonates ibandronate and clodronate, said Dr. Hortobagyi.

Another approach to treating bone metastasis is the use of recombinant proteins that can disrupt the process responsible for increased osteolysis. One such agent has recently been developed based on the soluble protein osteoprotegerin (OPG), which exists naturally in bones and helps maintain a balance between bone formation and bone resorption by preventing osteoclastogenesis. A commercial form of OPG is now in clinical trials, Dr. Hortobagyi said, and initial data suggest that it can be administered in very large amounts without causing any adverse side effects and may reduce bone resorption by 60% to 70% in patients with bone metastases.

A monoclonal antibody against the receptor for parathyroid hormone-related protein, which is produced by cancer cells to stimulate osteoclasts, is also showing promise. A multicenter phase I clinical trial of the antibody, temporarily known as CAL-02, has recently been completed. According to Aman Buzdar, M.D., Ashbel Smith Professor in the Department of Breast Medical Oncology and participating investigator on the trial, the antibody was fairly well tolerated with no unusual side effects. A multicenter phase III trial to determine the efficacy of CAL-02 compared with that of the bisphosphonate pamidronate is expected to start soon.

At M. D. Anderson, additional molecular therapies, including compounds similar to OPG and compounds that target the src oncogene (downstream of PDGFR in one of the bone metastasis-promoting pathways), are being studied in the laboratory and in the clinic for the treatment of bone metastasis. Also under study are molecular agents that can be attached to radionuclides and injected into the bloodstream to deliver systemic radiotherapy.

"There is a rich opportunity to explore various combinations of these agents for therapeutic advantage," said Dr. Hortobagyi. Several combination therapies are possible, including bisphosphonates with radionuclides or OPG and any of the new targeting agents with chemotherapy, a more traditional method of treating metastases.

Combination therapy is in fact necessary, emphasized Dr. Fidler, because of the heterogeneous nature of metastases. And as more therapies are developed, they will become more specific to the "highly selective, highly specific, yet highly predictable" mechanisms of metastasis.

"Eventually, every patient will be analyzed individually, and we will tailor treatment per patient, not per disease type. Not all bone metastases will be treated the same, because every patient is unique and every patient has a unique disease," said Dr. Fidler.

---

"...we think that cancer cells on the one hand and the endothelium of blood vessels in certain organs on the other hand have what I would call cellular addresses, and when the cellular addresses match, then the malignant cell settles in that organ."

— Gabriel Hortobagyi, M.D., chairman and professor, Department of Breast Medical Oncology
by Kerry L. Wright

Every day, Angela Hayes-Rodgers greets up to 20 new patients in the Breast Center with the same reassuring words: "I'm Angela," she says, "and I'm going to be your patient advocate. Whether you're an inpatient or an outpatient, anytime you come back, I'll still be your patient advocate. If you have any questions or concerns, please don't hesitate to give me a call."

After some conversation and questions, Hayes-Rodgers, a senior patient advocate in the Department of Patient Advocacy and Guest Relations at The University of Texas M. D. Anderson Cancer Center, pulls out her business card. She takes out a pink pen, the color of the Breast Center, and draws a star in the corner of the card before she hands it to the patient. "Just remember the card with the little pink star is my card," she says, "and I'm here to help you."

Hayes-Rodgers is one of 13 patient advocates—each assigned to at least one of the 27 care centers at M. D. Anderson—who work as liaisons between the patients and the different treatment centers, informing patients of the resources available to them, familiarizing them with how their particular care center is run, and helping to resolve any problems or concerns that arise during their course of care. Essentially, the advocates serve as a voice for the patients, listening to their concerns and relaying them to the appropriate person or department.

To be successful, a patient advocate must be a jack-of-all-trades, said Rhonda Hollins, one of three patient advocate coordinators who supervise and assist in the most challenging cases—cases that can begin trickling into the Department of Patient Advocacy and Guest Relations days, or sometimes only hours, after a patient arrives.

The duties of an advocate can include anything from tracking down lost eyeglasses, resolving scheduling difficulties, and solving communication problems to fielding complaints about the staff or about wait times in the clinic and finding answers to questions about billing or reimbursement. On average, advocates receive 10 to 15 messages from patients every day, and their goal is to return each call the same day and resolve the issues as quickly as possible.

Since some conflicts are more complex than others, the advocates must be prepared for anything. This means that they must understand the philosophy of patient care at M. D. Anderson, which includes knowing the patient's rights, the organization of the hospital, and the institutional policies, as well as be aware of all available services, including (just to name a few) the cafeteria, library, wellness center, business centers, and other support departments.

Each patient advocate is trained for one month, spending two days with each seasoned advocate, learning about each of the centers and observing colleagues at work. Training continues on the job, as advocates become more familiar with the services provided by the institution and learn their own style of interacting with the patients in their assigned care center.

As the problems that arise in the centers vary, so do the methods of resolution. If a physician is running late,
Department of Patient Advocacy and Guest Relations

For more information, call (713) 792-7776

for instance, an advocate may need only to validate the patient’s parking or offer a meal voucher. In other cases, more time and effort are required to reach a resolution.

“The there are at times conflicting points of view within families, and there are ethical issues that arise, so the advocates will request patient-care conferences or make a referral to the clinical ethics committee,” said Director of Patient Advocacy and Guest Relations Barbara Bowman.

Patient Advocacy Manager Joan Arnim remembers a case in which a patient with terminal cancer who had not responded to previous chemotherapy requested a treatment plan that included more chemotherapy. Because the patient’s disease was incurable and because of the potential harm to the patient, the plan was not supported by the patient’s primary physician or care center.

A consultation was called with the clinical ethics committee, which is composed of clinical ethicists, doctors, nurses, and additional staff members, often including those from the Department of Patient Advocacy and Guest Relations. The committee heard both sides of the conflict and, on the basis of professional integrity and the principle of “do no harm” to the patient, advised that additional chemotherapy not be administered. They also recommended a palliative care consultation and a range of psychosocial and spiritual resources. “The patient realized that there were other things being offered,” Arnim said, “and he accepted the committee’s recommendations.”

As a senior advocate, Hayes-Rodgers has been privy to many similar cases, often working with other advocates or members of other departments until each issue is resolved. Reaching those resolutions, she said, no matter how easy or difficult it may be, is one of the most rewarding aspects of her job.

The Department of Patient Advocacy was formally created in 1985 in response to the results of an institutional patient attitude survey in which some patients expressed an interest in having a place or a person they could call on to privately discuss a problem they were experiencing. In 1999, the departments of Patient Advocacy and Patient and Guest Relations merged to form the Department of Patient Advocacy and Guest Relations. Since its inception, the department has grown, and the advocates have become a resource not only for patients but also for physicians and staff.

“The patient advocates are bridges for information traffic both ways—from the patient to the physician and from the physician to the patient,” said Maria A. Rodriguez, M.D., an associate professor in the Department of Lymphoma and clinical medical director of the Lymphoma/Myeloma Center.

Some patients may have unrealistic expectations when they come to the hospital, said Dr. Rodriguez, especially of a center like hers, where the evaluation process is fairly extensive and it may take days for treatment decisions to be made. When a patient is frustrated or upset for this or another reason, physicians can request that a patient advocate visit the patient or be present during a physician-patient discussion. Other times, the patient advocates approach the physicians with concerns that the patients have shared with them but may not be willing to talk directly to their doctors about.

“We don’t want anyone to have
Patient Advocates Serve as Liaisons

(Continued from page 5)

complaints or problems, but when they
have complaints or problems, we want
them to feel comfortable and safe
enough to be able to say, 'I’m really
upset about this, and can you do
something to help me?’” said Arnim.
Having a staff member who is present
in the hospital but is not directly
involved in a patient’s treatment promotes
a sense of security, which is especially
important because many of the patients
at M. D. Anderson are away from home
and away from their primary care
physicians, said Dr. Rodriguez.

If it seems unlikely that so few
people could be responsible for so much
and still have time to make sure the
patients feel at home during their stay,
the secret is they have a little help.
About 30 experienced volunteer
advocates help provide inpatient
services—visiting patient rooms to
meet patients, describe the resources
available to them, and make sure that
their rooms are comfortable. If a patient
mentions a staff issue, the volunteer
then makes a referral to the appropriate
patient advocate for follow-up.

The Department of Patient Advocacy
and Guest Relations also oversees the
Greeter Program, through which staff
from all areas of the institution volun-
teer to meet, assist, and interact with
patients and their families for a few
hours in the morning, when the
patients first arrive at the institution.
According to Arnim, who trains
the greeters and has often worked as
a greeter herself, both the volunteer
advocates and the greeters work very
hard to make M. D. Anderson a very
personal and friendly place.

Said Arnim, “While I was greeting
patients once, a woman told me, ‘I
know M. D. Anderson is really a big
place and everything, but I feel like
I’m the only patient here.’”

“That’s our goal,” Arnim said.
Keeping the Heart Healthy in Patients with Cancer

Take a quick glance at recent health statistics, and it is easy to see that maintaining a healthy heart is no simple task. For those who have cancer, the task is even more difficult. Some cancer treatments can cause heart damage or aggravate underlying heart disease. However, there are preventive measures that can be taken to lower a patient’s risk of heart problems. Understanding the relationship between cancer and heart problems is an important first step in keeping the heart healthy throughout treatment and beyond.

Chemotherapy

Some chemotherapy drugs have been shown to cause heart damage in certain patients. Two drugs often associated with heart problems are doxorubicin and trastuzumab (Herceptin).

Doxorubicin

Doxorubicin, which is an anthracycline antibiotic, has been proven to be an effective agent against several types of cancer, particularly breast cancer. However, doxorubicin also can weaken muscles in the heart, and heart damage has been found to be a side effect of the drug. Specifically, the American Society of Clinical Oncology has found a risk of heart failure as high as 5% in patients who receive the highest recommended dose of doxorubicin and up to 20% when doxorubicin is given in combination with other chemotherapy agents or radiation therapy. (Heart failure is a condition in which the heart cannot pump blood effectively. Its symptoms include shortness of breath and fatigue.) Studies conducted at M. D. Anderson Cancer Center have shown that slow, prolonged, intravenous infusion of doxorubicin can significantly reduce the risk of cardiac problems.

Herceptin

Herceptin targets specific cancer genes and has been found to be very effective against breast cancer, particularly its deadlier forms. However, Herceptin can also damage the heart. Studies are still being done to determine the incidence of heart failure in patients who take Herceptin, but preliminary results indicate that the rate of heart failure increases significantly when Herceptin is taken along with other chemotherapy drugs.

WARNING SIGNS

The following signs typically indicate heart damage caused by chemotherapy:

- Puffiness or swelling in the hands and feet
- Shortness of breath
- Dizziness
- Erratic heartbeat
- Dry cough

Other Factors

As with any other type of stress, the stress associated with the diagnosis and treatment of cancer can be bad for the heart. In addition, existing heart problems, a history of radiation therapy to the mid-chest region, uncontrolled high blood pressure, and smoking increase the risk of heart damage in patients with cancer.

Prevention

Tests of heart function performed before chemotherapy begins can keep patients from suffering potentially harmful side effects. Also, during chemotherapy, physicians routinely perform heart function tests, such as an electrocardiogram; if problems are detected, chemotherapy may be stopped to prevent serious damage.

Everyone, including patients with cancer, can take the following steps to reduce the risk of heart disease:

- Maintain a diet low in saturated fats and cholesterol
- Avoid smoking and exposure to secondhand smoke
- Control high blood pressure
- Avoid obesity
- Increase physical activity
- Control diabetes

Following the advice of physicians and the guidelines for heart health is recommended for everyone, but it is especially important for patients with cancer. Don’t be a statistic: do what you can to prevent heart disease.

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.

February 2002

©2002 The University of Texas M. D. Anderson Cancer Center
Patient Advocates:
Solving Problems and Building Bridges

Charles F. Levenback, M.D.
Associate Professor
Department of Gynecologic Oncology

In many ways, patient advocates personify what is best about M. D. Anderson Cancer Center. By taking the time to talk to every new patient, the advocates convey the message that we at M. D. Anderson care about patients as individuals. Patient advocates, by their very existence, are also an acknowledgment that we aren’t perfect and that things sometimes can and do go wrong, but we care enough to want to know when our patients are having problems and to do our best to solve them.

Like all patient advocates at M. D. Anderson, Sarah Marvel, our advocate in the Gynecologic Oncology Center, is an important resource for patients, but she is also invaluable to me and the other physicians in the center.

I call on Sarah in a variety of situations. When a patient has trouble with scheduling or billing, I ask Sarah to help her navigate the “system.” Sometimes, a patient has a complaint about how she was treated in another area of the hospital. Other times, patients just need a little extra time from the staff—time that the pressures of a busy clinic prevent me from being able to give them. Occasionally, I realize that I did not meet a patient’s needs in a particular situation, and I call Sarah to step in and help me make amends.

I hear from Sarah all the time. She follows up on the patients and reports on her progress with solving a problem or alerts me about a new issue. When someone complains about me, I usually hear it from Sarah. I know this is often difficult for her, but I view it as vital to my efforts to continually improve my job performance. Sometimes Sarah, at the patient’s request, has to help reassign a patient from one doctor to another. Somehow she always manages to accomplish this feat without ruffling feathers.

Before coming to M. D. Anderson, I was on the faculty at institutions that did not have patient advocacy programs. Without advocates to serve as mediators between the doctors and the patients, there was the tendency to develop an “us versus them” mentality: the patients against the staff. Patient advocates help keep the lines of communication open and defuse problem situations before they get out of hand.

Like all good patient advocates, Sarah is always looking for solutions that will benefit everyone involved. By making sure that the patients’ needs and wishes are expressed each and every day, Sarah is an integral part of our patient care team.