Multidisciplinary approach a new paradigm for cancer care

M. D. Anderson leads the fight against bone pain from metastatic cancer

Say the word "cancer" and many people think "pain." It is true that severe pain is a fact for some cancer patients. The pain is usually caused by the tumor invading sensitive tissues. The bones are one of the most common sites of cancer metastasis, and because of the dense concentration of nerves around the bones, one of the most painful. But patients with this metastatic bone pain can now find relief, thanks to a special clinic recently launched at The University of Texas M. D. Anderson Cancer Center.

Metastatic bone pain is often incapacitating. Patients with this pain are usually unable to care for themselves, work, drive, or enjoy daily activities. They are dependent on friends and families. Unfortunately, common cancers such as those of the prostate, breast, and lung often spread to the bone, so the problem is widespread.

Patients with metastatic bone pain are treated with radiation, analgesics, or surgery, usually in combination. But each patient's pain is different, and physicians who treat this pain have begun to realize that an individualized, tailored treatment strategy works best. Such an approach is possible only when these specialists come together, sharing their expertise to evaluate a patient's case and develop a treatment plan. This multidisciplinary team approach is helping win the fight against metastatic bone pain at M. D. Anderson.

Relief of metastatic bone pain is a very complex and difficult clinical problem," said Nora Janjan, M.D., associate professor in the Department of Radiotherapy and co-founder of the multidisciplinary metastatic bone pain clinic. "It is also very costly, to the patients who suffer and are incapacitated, to the family members who must stay home and care for the patient, and to society as a whole, which loses productive people. And none of this is necessary, because we can control cancer pain."

By the time patients come to M. D. Anderson for pain treatment, most have had all of the standard therapies. Their pain often makes the slightest movement distressing. Most were overcome by the effort of visiting several different clinics: one for radiotherapy, one for chemotherapy, and others for pain assessment and orthopedic and neurosurgical evaluations. What was most difficult, said Janjan, was that it was sometimes difficult or impossible for these patients to receive their prescribed radiotherapy because they could not tolerate the treatment position.

"We’re here to heal patients, not hurt them. We started this multidisciplinary clinic just over a year ago especially for these patients whose pain is getting in the way of their treatment," said JanJan. The clinic is located in the radiotherapy area. For their initial evaluation, "all the specialists come together, review the treatment options, develop a coordinated treatment plan, and present their recommendations to the patient. The patients stay in one clinic, eliminating a lot of the moving around at M. D. Anderson and the travelling back and forth from home. This is a big relief for the patients and for the family members who must accompany them." The team includes co-founder Richard Payne, M.D., chief of the Section of Pain and Symptom Management, Department of Neuro-Oncology; Herman I. Libschitz, M.D., Department of Diagnostic Radiology; Donald A. Podoloff, M.D., Department of Nuclear Medicine; Theresa Gillis, M.D., Director of Physical Medicine and Rehabilitation, Department of Neuro-Oncology; Alan Yasko, M.D., Department of Surgical Oncology; Samuel Hassenbusch, M.D., Ph.D., Department of Neurosurgery; Richard B. Patt, M.D., Department of Anesthesiology and Critical Care; and the medical oncologists on the case.

continued on page 2
"We have a very practical, effective strategy for relieving this pain."

The team approach to stopping pain

"Radiation is the standard therapy for metastatic bone pain because it controls the tumor that is causing the pain," explained Janjan, "but many other specialists come into play. Dr. Libschtz helps pinpoint the exact cause and site of the pain, and Dr. Payne develops strategies to control the patients' pain so that they can undergo the therapy. Dr. Podoloff evaluates the extent of bone involvement with bone scans and assesses the potential of radiopharmaceuticals such as strontium-89 in treating the pain. Dr. Hassenbusch evaluates the utility of neurosurgical techniques.

"Dr. Yasko and Dr. Gillis are important members of the team because metastasis can weaken the bones, putting the patients at risk of spinal cord compression and fractures. Dr. Yasko assesses the need for surgical stabilization of the bone, which is often necessary when critical sites like the hip are involved or if pain persists after radiotherapy. If surgery is not required, Drs. Yasko and Gillis evaluate ways to reduce the patient's risk of fracture.

"The team approach really works for our patients. Our breadth of expertise and coordinated review of clinical findings allows the team to pick up subtle signs that one physician alone might miss. Together, we are able to offer effective interventions."

Of the 270 patients who visited the clinic in its first 14 months, about 60% had their treatment plan altered after their evaluation. Over 70% had their pain medications adjusted in some way, usually the schedule or the route of administration.

At the root of the clinic’s mission is concern for patients’ quality of life. For these patients whose cancer has progressed to the point at which it causes bone pain, a cure is usually not possible. "Controlling cancer pain allows us to administer treatment while improving the patient’s functioning and quality of life," said Janjan. One key to the team’s success is its respect for what the patient can tell them about his or her pain. She went on, "The location of their pain reliably tells us where the disease is, and that guides us in determining which diagnostic studies need to be done and what kinds of treatment might be most effective. We listen very closely to what they say about their symptoms, and once we figure out what is causing these symptoms, then we have a specific strategy for managing the pain and the cancer."

Education cuts through barriers to pain control

Part of the team’s role is educating patients and their families—letting them know that pain is part of metastatic disease and can be controlled. Patients and their families also learn that it is all right to be treated with analgesic drugs for cancer pain. Many people want to avoid strong analgesics such as morphine. Fear of addiction and a feeling that these drugs should be "saved" in case the pain gets worse have led to widespread undertreatment of cancer pain, reported Payne (see box).

Janjan and Payne insisted that these myths about cancer pain must be dispelled. “Most people equate cancer with suffering,” said Janjan. "If we could eliminate that belief, people would not be afraid to undergo cancer screening and to find their cancer earlier, when it can be treated and cured. They would not be driven to extremes such as suicide and euthanasia, to relieve their suffering."

The multidisciplinary approach is possible, reported Payne, only where all the specialists are available under one roof. “I believe the multidisciplinary metastatic bone pain clinic is an absolutely unique resource in this country,” he reported. “I don’t think there is any other cancer center that has a large enough volume of patients to make this possible. Although metastatic bone pain is very common, there aren’t many centers that have the local expertise to support such a clinic.” He and other team members have begun videotaping some

Current Metastatic Bone Pain Protocols

RT 94:047 ....... A Phase III randomized study comparing conventional palliative radiation (30 GY/10 fractions) with single-fraction photon radiation (6 or 8 GY) for bone metastases in patients receiving systemic therapy (Study chairman: Dr. Janjan)

RT 94:032 ....... A Phase III randomized study comparing conventional palliative radiation (30 GY/10 fractions) with single-fraction photon radiation with or without strontium-89 for painful bone metastases (Study chairman: Dr. Janjan)
of their cases for educational purposes, and they will be presenting their experiences at the annual meetings of the American Society for Clinical Oncology, the American Pain Society, and the American Society for Therapeutic Radiology and Oncology.

Meanwhile, Janjan, Payne, and their colleagues are conducting research to improve their treatment of metastatic bone pain. Clinical trials of new treatments are offered through the clinic. Whether they receive a standard treatment or an experimental one, however, patients leave the clinic with something many had lost—hope. "The multidisciplinary clinic is not only good for the patients, it's good for us who treat the patients. There's less confusion about each patient's care, because we're a cohesive unit in treating these patients. We feel we have a very practical, effective strategy for relieving their pain and making them comfortable both during and after therapy," said Janjan. "We believe that controlling the pain while we control the tumor is absolutely critical."

—KATHRYN L. HALE

Referrals. Physicians who have questions or would like to refer a patient may write Dr. Janjan at the Department of Radiotherapy (Box 97) or Dr. Payne at the Department of Neuro-Oncology (Box 100), The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, or call (713) 792-3432 (Janjan) or 792-2824 (Payne).

ALL NEW PATIENTS AT M. D. Anderson fill out a pain inventory. Among patients referred to the multidisciplinary metastatic bone pain clinic, over 70% reported that they had moderate to severe pain, and over 25% reported severe pain. Over half said their pain was not adequately controlled. The undertreatment of cancer pain is not a myth, said Richard Payne, M.D., co-founder of the clinic. Many patients fear that the drugs will lose their effectiveness if used "too soon," but the biggest barrier to appropriate drug treatment of cancer pain is fear of addiction.

Studies in thousands of patients at many major cancer centers have shown that addiction to pain medications in cancer pain patients is a nearly nonexistent risk, said Nora Janjan, M.D., co-founder of the clinic. "Addiction is a behavior, not a physiologic response," said Janjan. "What we think of as an addict is someone whose desire for drugs overwhelms everything they do, how they live. Our patients don't do that. In fact, once the cause of the pain is treated, most patients will take themselves off the drugs. There is something called pseudoaddiction, when a patient's pain is so severe that he desperately goes from one physician to another, trying to get enough medicine to control his pain. Once he gets adequate medication, that behavior stops."

Many physicians are not aware that concepts of cancer pain management have changed in the last few years and that it is now considered good medical practice to prescribe drugs such as morphine for cancer pain. Payne cited cases of patients who lived in fear that their hometown physician would not continue writing prescriptions for their pain medication or that the local pharmacy would not stock the drugs. For this reason, he and other members of the multidisciplinary metastatic bone pain team work with a patient's local physician to develop a treatment plan for the patient. "Once physicians understand the medical reasons for prescribing these drugs," said Payne, "they are usually very willing to continue writing the prescriptions. The M. D. Anderson physicians will document our recommendations for drug treatment in the patient's medical record, giving support should the local physician's practice be audited by the Drug Enforcement Administration."

"The State of Texas is unique in this country," said Payne, "because, thanks largely to the efforts of Dr. Stratton Hill here at M. D. Anderson, we have as part of our Medical Practice Act something called the Intractable Pain Treatment Act, which reinforces the concept that the physician's major responsibility is to treat pain and suffering and recognizes the legitimacy of opiate therapy to do that. Each case of suspected abuse is still reviewed separately by the state Board of Medical Examiners, but physicians in Texas do have legal protection for prescribing these drugs. There's a movement abroad to go to each state legislature and medical examining board to get similar laws passed in all states. But this requires education, establishing a dialogue with the people who make and enforce the laws."
Cancer cells do not behave like normal cells. Different genes are activated, and different types of cancer cells behave differently from each other. A variety of proteins are produced by cancer cells; these differ by organ and cell type and by the extent of the tumor. These characteristic genes and proteins can be used to identify, or mark, specific cancers, and much work is being done in laboratories and clinics to find and identify them.

A marker would be particularly helpful to urologic oncologists in treating patients with bladder cancer, said H. Barton Grossman, M.D., professor in the Departments of Urology and Cell Biology at M. D. Anderson Cancer Center. Grossman hopes protein or gene markers of bladder cancer will enable earlier detection and more accurate assessment of patient prognosis.

Grossman and colleague Monica Liebert, Ph.D., associate professor in the Departments of Urology and Cell Biology, began collaborating on bladder cancer research about 10 years ago at the University of Michigan. They were both interested in the role of monoclonal antibodies in defining new bladder tumor antigens. "More recently, we've both become interested in using molecular techniques to study genes that play key roles in bladder cancer," Grossman said. They moved their laboratory to M. D. Anderson about a year ago.

Much of their research is funded by the National Cancer Institute, which has created a cooperative group called the Bladder Cancer Network specifically to study bladder cancer markers. M. D. Anderson is one of six institutions currently involved.

Prognostic markers would guide treatment

Bladder cancer, the fifth most common type of cancer in the United States, has two distinct forms: superficial disease, which includes early stage, localized cancers, and invasive disease, which includes more advanced tumors or those that have spread. Most patients have the superficial form of bladder cancer, which poses little threat of metastasis. With careful management and close follow-up, most of these patients do well for long periods of time. Although they may have recurrences of disease in the bladder, only a small proportion of patients will develop invasive disease.

Patients with the invasive form of bladder cancer have a much greater chance of developing metastases and eventually dying of their cancer. Thus, these patients are treated more aggressively, frequently with resection of the bladder and urinary diversion.

"For both groups of patients, it is very difficult to tell up front who is going to do well and who is not," Grossman said. "If we had markers that would give us that information, we would know when we could safely lessen the intensity of treatment. For example, patients with superficial bladder cancer whom we knew had a good prognosis could be treated with endoscopic (transurethral) resection alone and perhaps wouldn't need cystoscopic follow-up quite so often." Patients whose tumors were more likely to become invasive would be treated more aggressively, with intravesical chemotherapy or immunotherapy, to try to prevent this progression. "Similarly, if we knew which patients with invasive cancer had a relatively low chance of developing recurrent cancer and metastases, they could be treated with cystectomy alone," Grossman said. Patients at higher risk of developing metastatic disease would be treated with aggressive adjunct chemotherapy strategies to try to prevent the progression.

The current means of predicting outcome lack precision, Grossman said. Clinical parameters such as disease stage, tumor grade, and whether tumors are multifocal are prognostic factors in studies of groups of patients, but they are not very predictive for individual patients. For example, most, but not all, patients with multifocal disease have a cancer that will probably recur.

Through their work with monoclonal antibodies, Grossman and Liebert have found a marker that may correlate with survival duration for patients with bladder cancer: α6β4 integrin. Integrins are transmembrane proteins that act as receptors for extracellular matrix proteins. α6β4 integrin is normally expressed only in the basal layer of the urothelium but seems to be overexpressed in many bladder cancers. Liebert and Grossman and col-
leagues examined frozen sections of bladder tumors, urine specimens, and bladder wash specimens from 59 patients, comparing the α6β4 integrin levels with the patient outcomes. Patients with the invasive form of cancer who strongly expressed α6β4 had a significantly shorter survival time than patients who expressed α6β4 weakly or not at all. The question remains as to whether this marker is an independent prognostic indicator; will it provide more information than clinical indicators such as stage and grade? Answering this question will be the next step in Grossman and Liebert’s research.

**Tumor markers would aid diagnosis**

Grossman and Liebert are studying a second marker, DD23, which appears to be very accurate for detecting bladder cancer cells in urine and bladder wash specimens. Unlike integrin α6β4, whose level of expression might be helpful in predicting individual patient outcome, DD23 would be useful in detecting tumors in the first place. This research is being done in collaboration with investigators at the University of Oklahoma, one of the other institutions in the Bladder Cancer Network. DD23 is essentially not expressed in normal bladder tissue but is significantly overexpressed in bladder cancer. “We’ve seen DD23 protein expressed in cystectomy specimens in grossly normal areas of tissue separate from the tumor,” Grossman said. “We think that this may represent very early neoplastic transformation that isn’t detectable by standard histologic evaluation.” A DD23 test should become commercially available in the future.

Because DD23’s expression seems to increase very early in cancer development, interest has arisen in testing DD23 as a surrogate end-point marker in chemoprevention trials. When an agent such as 4-hydroxyphenylretinamide (4-HPR) is tested to see whether it can help prevent cancer from developing, the classic end points of the trial are tumor occurrence or recurrence or death. Although these are clear, objective end points, it can take years to obtain this information. In fact, the better the therapy is, the longer it takes to get the results of the study. The National Cancer Institute is thus increasingly interested in looking at surrogate markers for conventional end points. For example, prostate-specific antigen, or PSA, is being evaluated as a surrogate marker in trials of therapeutic and chemopreventive agents for prostate cancer.

An upcoming study of 4-HPR in bladder cancer will determine whether a lack of expression of DD23 correlates with lack of recurrence and with longer survival. “If we can see that an increase in DD23 expression correlates with tumor recurrence, but appears long before tumor recurrence, then in future studies we could just look for changes in DD23,” Grossman said. “We could get an answer in six weeks rather than waiting six months or several years.”

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**Current Bladder Cancer Protocols**

- **URL 93-003** ..... A pharmacology-based efficacy trial of intravesical mitomycin C in bladder cancer interactive pharmacology studies (Study chairman: Colin P. N. Dinney, M.D.)
- **URL 94-002** ..... A Phase II study: intravesical AD 32 in patients with transitional carcinoma of the bladder (Study chairman: Colin P. N. Dinney, M.D.)
- **DM 86-083** ..... A randomized trial of preoperative versus postoperative chemotherapy for invasive bladder cancer (Study chairman: Christopher J. Logothetis, M.D.)
- **URL 94-004** ..... A Phase III study of oral bopirimine versus intravesical bacillus Calmette-Guérin (BCG) in adult patients with BCG-naive bladder carcinoma in situ (Study chairman: Louis L. Pisters, M.D.)
- **DM 92-025** ..... A prospective randomized trial comparing FAP (5-fluorouracil, doxorubicin, and cisplatin) to MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) chemotherapy for patients with advanced metastatic urothelial tumors (Study chairman: Christopher J. Logothetis, M.D.)
- **DM 94-051** ..... A Phase II open study of intravenously administered tirapazamine plus cisplatin in subjects with transitional cell carcinoma of the bladder refractory to prior therapy (Study chairman: Shi-Ming Tu, M.D.)
Interactive video
continued from page 8

patient educators, and educational specialists. The presentation combines texts, tables, illustrations, videos, animation, and music to deliver comprehensive yet comprehensible messages about breast cancer.

The videos feature eight women who speak candidly about their personal experiences with breast cancer, the surgical treatment options they chose, and their lives since surgery. “This is probably one of the more popular features of the system,” commented Karen Adsit, Ed.D., Department of Instructional Development. “For some patients, the videos are almost like a live discussion with women who have survived. They think ‘Here is a woman who has gone through exactly what I’m about to go through.’ It’s a real person talking about a real situation, and it is more appealing than screen after screen of words and pictures.”

A range of information offered

The program begins with a general menu that branches into several subcategories that have even further subcategories. The patient can begin with any topic she chooses and does not have to cycle through unwanted information. Commenting on the versatility of the program, Singletary said “Choices” has a broad appeal. “Different patients will start out with different levels of knowledge about breast cancer. Some may be ready to go straight to the discussion about treatment, whereas some may need to start with a discussion of the disease itself. This program is user-driven so the patient can start where she feels most comfortable. Likewise, the patient can review portions of the program repeatedly until she gains a comfort level with a particular topic.”

Hands-on, self-paced instruction

Interactive instruction is not new, nor is videodisc technology; however, combinations of these techniques have only recently been applied within the medical arena, and the “Choices” program is believed to be among the first of its kind in the country. According to Singletary, there are a host of benefits to hands-on, self-paced instruction. “This type of instruction allows patients to take charge of the learning process, which means they usually approach the learning task more aggressively and with a more positive attitude. The information they gain enables them to formulate intelligent questions when they consult with the physicians and surgeons.”

There are several other benefits to this system. The information that patients receive is consistent, and the words and visuals used to describe procedures are the same all the time; this stimulates recall. Because the patient has to respond physically to make inquiries, she is more apt to retain information; and because she is operating the system in total privacy, she does not have to consider any inquiry “stupid” or feel embarrassed by the menu topics she chooses to review. These factors all help the patient learn.

The “Choices” kiosk is conveniently located within the breast cancer clinic in an area that affords the patient privacy and a relaxed atmosphere. A big plus for patients is that the system is easy to learn. “You don’t have to be a computer expert,” commented Adsit. “If you can point and touch, you can easily operate this system.” Although the system was designed primarily for use by patients, it is also available for family members and friends. Said Adsit, “The feedback has been very positive. Patients have commented that the system is easy to use and informative, and they feel better prepared to make decisions when they consult with the surgeon.”

—VICKIE J. WILLIAMS

Referrals. Physicians who have questions or would like to refer a patient may write Dr. Singletary at the Department of Surgical Oncology (Box 106), The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, or call (713) 792-6937.
Bladder cancer
continued from page 5

ddRT-PCR technique isolates genes expressed in cancer

In addition to monoclonal antibody techniques, Liebert and Grossman are also using the differential display reverse transcriptase–polymerase chain reaction (ddRT-PCR) technique to look for genes whose expression is altered in bladder cancer. Using this technique, they are comparing genes in undifferentiated and differentiated cells with the same genetic backgrounds. They have found some novel genes that seem to be expressed only in differentiated cells. They also found a gene, called MAL, that had formerly been thought to be expressed only in T-lymphocyte cells, not in urothelium. The next question is, will expression of these genes be decreased in bladder cancer, in which cells revert to a less differentiated form? Liebert and Grossman have found that this is the case with the MAL gene. They are going to continue to study this gene to see if it has any prognostic significance in bladder cancer.

“We are hoping to find genes that are interesting from a diagnostic or prognostic standpoint,” Grossman said. It is also possible that one of these genes could eventually be used as a therapeutic target. “If you have a gene that is expressed in normal bladder cells but not in bladder cancer cells, perhaps you could induce reexpression of that gene in the bladder cancer cells,” he said. “We may not be able to convert a cancer cell to a normal cell—but if we could convert an aggressive cancer cell to a more benign form, it would be a significant accomplishment.”

Tumor suppressors also targets for gene therapy

Another M. D. Anderson researcher who is looking for a gene with therapeutic potential in bladder cancer is Jer-Tsong Hsieh, Ph.D., assistant professor in M. D. Anderson’s Urology Research Laboratory. Hsieh and David I. Kleinerman, M.D., an M. D. Anderson fellow in urology, are assessing strategies based on these prognostic markers,” he said. “We think they will show us which patients need aggressive therapy and which don’t.”

—SUNITA PATTSON

Bladder cancer fascinating model of disease

Bladder cancer is a very good model for experimental gene therapy, Grossman said. “It’s a fascinating model of disease.” First, it is a classic environmentally induced cancer that is clearly associated with carcinogens and smoking. Its behavior fits the model in which a carcinogen is excreted in the urine and sits in the bladder, causing multifocal disease. Second, the bladder is very accessible; it can be easily studied, and agents can be easily applied to the urothelial surface through a catheter.

In addition to working in the laboratory, Grossman is also the director of clinical research in the Department of Urology. “One of my goals here is to foster and develop the clinical research protocols at M. D. Anderson, to try to bring the laboratory advances and clinical medicine together,” he says. He and Liebert continue to look at the tumor tissue specimens from his patients in search of markers that will determine each patient’s prognosis. “We hope to develop some novel treatment strategies based on these prognostic markers,” he said. “We think they will show us which patients need aggressive therapy and which don’t.”

—SUNITA PATTSON

Bladder cancer fascinating model of disease

Bladder cancer is also expressed in normal bladder urothelium, the investigators decided to try introducing C-CAM1 into bladder cancer cells in mice. As in the prostate, the resulting increased expression of C-CAM1 suppressed tumor growth. “Our preliminary data provide compelling evidence that C-CAM suppresses cancer development,” Hsieh said. “We want to find out whether C-CAM could be a candidate for intravesical therapy.” Their next goal is to determine the optimal dosage of the C-CAM1 adenovirus for inhibiting bladder cancer growth in mice.
Interactive computer technology puts information at patients’ fingertips

New computer program enhances the surgeon-patient consultation

More than 850 women undergo surgery for breast cancer at The University of Texas M. D. Anderson Cancer Center each year. As part of the standard procedure, each surgery candidate spends several hours in consultations with surgeons and other health care professionals reviewing treatment options, surgical procedures, and associated risks. The goal is to provide each patient with the information she needs when deciding which procedure is best for her, said Eva Singletary, M.D., chief of breast surgery at M. D. Anderson, but often the stress associated with a diagnosis of breast cancer and impending surgery is compounded by the frustration of having to deal with mountains of complex medical information. “It can be quite a shock for a woman to learn she has breast cancer,” said Singletary. “Her anxiety becomes even worse when she has to decide how to combat the disease.”

In early 1994, the breast cancer staff at M. D. Anderson began considering ways to streamline the consultation process while improving its efficiency and ensuring that patients were well informed. Their solution was an innovative computer system recently put into place at the center. The system offers user-driven, self-paced instruction based on interactive videodisc technology. By touching the screen, patients can choose to view a range of information about breast cancer. The system literally puts information about breast cancer at the patient’s fingertips and presents it in an appealing manner that motivates the patient rather than intimidating her.

“We developed this system to help alleviate some of the fears associated with the diagnosis and to enable breast cancer patients to make informed decisions, with the surgeon, about surgical treatment options,” Singletary explained.

Program includes videos of eight patients

The computerized system can be operated while standing or sitting, and operates by touch command, much like an ATM machine. The multimedia program, entitled “Choices: Breast Cancer Treatment Options,” was developed through the cooperative efforts of patients, surgeons, nurses,