Experts Recommend Treating Cancer Pain in the Context of Other Symptoms

by David Galloway

When renal cell carcinoma metastasized to his lungs and bones, the pain was so severe that it clouded every aspect of his life.

Mr. [redacted]’s wife, [redacted], felt helpless to allay her husband’s suffering. “When a person is in a lot of pain, it is like he doesn’t care anymore about anything. He cannot eat; he cannot enjoy watching TV; he cannot enjoy talking to his family,” said Mrs. [redacted] whose husband died in August 2003. “When he was in pain, it was terrible, because pain makes a person very weak. You don’t have anything at all left, no energy, nothing.”

As the [redacted] learned, however, pain is no longer something that patients with cancer must simply learn to live with. Mr. [redacted]’s pain and other symptoms were alleviated through a combination of supportive care, medications, and spinal nerve blockade.

Researchers now consider pain to be just one part of a matrix of symptoms to be assessed and treated as a whole. Pain is interwoven with fatigue, nausea, depression, anxiety, drowsiness, shortness of breath, loss of appetite, insomnia, and a diminished sense of well-being. In essence, clinicians are beginning to learn and apply what, on some level, patients have always known: the

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Treating Cancer Pain in the Context of Other Symptoms

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experience of pain is as varied as the people who suffer from it. “What I call pain is not the same thing as what [REDACTED] calls pain,” said Eduardo Bruera, M.D., chair of the Department of Palliative Care and Rehabilitation Medicine at The University of Texas M. D. Anderson Cancer Center. “For me, pain is clearly afferent noxious stimulation by the spinothalamic tract into the somatosensory cortex. [REDACTED] calls pain something completely different. It’s the pain that he has in the back, his fears, his losses, his worries. All those things are part of what [REDACTED] sees all the right in the world to call pain. His doctors cannot run away and steal the word.”

Asking patients about their pain and other symptoms is important. A group led by Charles Cleeland, Ph.D., chair of the Department of Symptom Research, has reported that some patients do not complain of pain or other symptoms because they may not want to distract the physician from treating the primary disease, may think of pain as an inevitable part of having cancer, or may not want to acknowledge that their disease is progressing. Many fear that they will lose mental control, become addicted, or have unmanageable side effects. Some patients also fear that early pain control will preclude pain control later in the disease because of concerns (which their physicians share) that they will become tolerant of pain medications.

At M. D. Anderson, pain and other symptoms are treated by a team of doctors, nurses, nutritionists, physical therapists, occupational therapists, counselors, social workers, and others, Dr. Bruera said. Using that approach, he said, it is possible to alleviate not only pain but also a whole array of symptoms in most patients, and relieving those other symptoms can, in turn, help to lessen a patient’s pain.

Often, when cure is an option, a patient’s surgical pain can be managed by standard postoperative pain medication administered by an anesthesiologist. Other patients, however, might experience burning pain in the area of radiation therapy, painful mucositis associated with high-dose chemotherapy or radiation therapy, or a pinched nerve as a result of tumor growth. In most cases, these patients are treated with opioid painkillers and adjuvant drugs to manage their pain while they are undergoing cancer treatment. Whether the pain is caused by the cancer or by the treatment, the completion of successful cancer treatment is usually accompanied by a rapid decrease in pain and progressive discontinuation of the medication. However, Dr. Bruera said, in some cases, pain caused by damage to nerves or to bone will linger beyond the completion of treatment. In those cases, the patient will need to be seen in a chronic pain clinic.

For patients whose cancer cannot be cured, “we need to then prepare for pain being part of their life for the remainder of their life,” Dr. Bruera said. “And therefore, our management needs to be much more comprehensive.” In some cases, pain can be eliminated completely. For example, if a patient has a painful metastasis, radiation therapy can sometimes shrink the tumor enough to eradicate the pain. Sometimes, the pain cannot be eliminated but can be controlled quite well with medications. For those patients, the pain management team develops plans for ongoing treatment.

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**PROTOCOLS**

**Studies Examine Treatment for Cancer-Related Pain**

Clinical trials in progress at The University of Texas M. D. Anderson Cancer Center include the following for adult patients with cancer-related pain.

- **Phase I psychophysical study of cancer- and chemotherapy-induced pain (ANS00-339).** *Physician: Patrick M. Dougherty, Ph.D.*

  Patients of either sex under treatment by the Pain Service for pain that developed as a result of cancer therapy with vinca alkaloids, taxanes, platinum-based compounds, or ionizing irradiation are eligible.

- **Patients without pain who are just beginning chemotherapy with taxanes or platinum-based compounds are also eligible.**


  Patients with a local recurrence of rectal cancer or concurrent distant metastatic disease are eligible. Patients are not eligible if they have pathologically confirmed disease other than adenocarcinoma (i.e., squamous cell carcinoma of the anus, cloacogenic tumors), a concurrent pelvic malignancy in addition to rectal carcinoma, or a history of either a documented pelvic pain syndrome or a documented preoperative diagnosis of chronic constipation.

- **Phase III study of preoperative rofecoxib combined with patient-controlled epidural analgesia for postoperative analgesia following thoracotomy for lung resection (ID02-193).** *Physician: Peter Norman, M.D.*

  Patients who are scheduled to undergo a unilateral thoracotomy with standard incision and postoperative epidural analgesia are eligible. Exclusion criteria include an allergy or reaction to non-steroidal anti-inflammatory drugs, peptic ulcer disease, chronic use of analgesics, and chronic pain syndromes.

- **Pain quantification and management for standard interventional radiology procedures with subsequent patient satisfaction analysis (ID02-374).**
The first line of treatment for pain is still opioid drugs, Dr. Bruera said. "Amazingly, morphine was developed more than 200 years ago, and it is still the main analgesic we use, or a synthetic cousin that works the same way," he said. The recreational use of opioid drugs causes concern for some patients, however. "Some patients probably even deny themselves pain relief because they have heard about these drugs in the newspaper," said Dr. Cleeland. Although opiates can cause sleepiness, nausea, constipation, and other problems, adjuvant drugs can reduce or eliminate those problems while still allowing good pain control.

"While in most cases the pain can be controlled by relatively straightforward methods, some patients have severe pain that is resistant to these methods," said Allen Burton, M.D., chief of the Pain Management Anesthesiology Service. "In patients with refractory pain, other options such as nerve blocks, subcutaneous or spinal infusions, palliative radiation or chemotherapy, and even palliative surgery may be used in careful combination to offer optimal patient quality of life."

Dr. Charles Cleeland (center), chair of the Department of Symptom Research, discusses the results of a pain study with Dr. Karen Anderson (left) and Dr. Shelly Wang, assistant professors in the department. In the study, they examined the relationship between an inflammatory cytokine (interleukin-6) and the average severity of multiple symptoms over time during bone marrow transplantation. They found that both the severity of symptoms and interleukin-6 peaked during the nadir of therapy.

According to Dr. Bruera, researchers in the past decade have learned that treating pain alone is not enough, because patients with cancer experience pain intertwined with other symptoms. "It is completely different when you have pain alone—lower back pain or chronic headache, things that happen as the main problem—compared to when pain happens in the context of a major health problem."

At M. D. Anderson, clinicians and researchers are interested in understanding the constellation of symptoms that patients experience and their severity. Patients are asked to rank their symptoms on a scale of zero (no effect) to 10 (worst imaginable). The questionnaire can be completed in just a minute or two, and it gives doctors and nurses much more information than can usually be gleaned from just talking with patients. In fact, when the scale is not used, patients will consistently fail to volunteer all their symptoms. "It very much depends on the personality of the patient," Dr. Bruera said. "Some patients are very outspoken, outgoing, and they will just pour out a litany of symptoms. Some patients will be much more withdrawn and unlikely to complain. By giving them a structured series of symptoms, we are able to see how many there are and the intensity and so on."

On that zero-to-10 scale, seven seems to be a critical cutoff point. "When patients say their pain or their fatigue reaches a level of seven, it is pretty much overwhelming. It is the total focus of their attention. It robs them of time with their family. It robs them of activities. It robs them, really, of enjoyment of life in general," Dr. Cleeland said.

Much of the progress in pain management has occurred within the past decade, after an Eastern Cooperative Oncology Group study showed that about 40% of patients were not getting sufficient treatment for their pain. "It was equivalent to a pain of seven being treated by an aspirin," Dr. Cleeland said.

Dr. Cleeland cited a multi-institutional study that showed pain at a level of three interferes with a patient's enjoyment of life. At level four, it interferes with work. At five and six, it affects activity, mood, and sleep. At seven, it hinders a patient's ability to walk. At eight, pain makes it difficult for a patient to relate to loved ones. A study of 527 patients at M. D. Anderson (Continued on page 4)

Physician: Frank Morello, M.D.
The goal of this study is to measure and record patients' pain levels before, during, and after standard interventional radiology procedures. Patients must live in the United States and speak English. Patients undergoing procedures performed under monitored anesthesia care or general endotracheal anesthesia will not be eligible.

For more information about these clinical trials, physicians and 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) 792-3245. Visit the M. D. Anderson Cancer Center clinical trials Web site at http://www.clinicaltrials.org for a broader listing of treatment research protocols.
showed that one in five outpatients rated their pain as seven or higher.

Researchers are now studying how various symptoms might be linked together. “A lot of these symptoms that occur together seem to be related to an inflammatory response to the therapy for cancer,” Dr. Cleeland said. The insult of therapy generates cytokines, which appear to cause not only pain but also lethargy, loss of interest, diminished learning capacity, and other problems in animal models. If these results translate to clinical studies, as expected, the treatment of symptoms could be simplified. “Patients with seven or eight symptoms may not need to take seven or eight drugs,” Dr. Bruera said.

Some of the changes in pain management are the result of changes in physician attitudes toward cancer treatment. “Before, we thought that all the problems that our patients had were brought on by the cancer,” Dr. Bruera said. A person was considered healthy until cancer struck, and all subsequent problems were blamed on the cancer. Now, oncologists are paying more attention to premorbid conditions, such as chronic depression, alcohol abuse, personality disorders, fatigue, and chronic infections. “And cancer comes on top of that,” Dr. Bruera said. “So all these symptoms and disease problems are a consequence of both the cancer and what was there before.”

For patients like [ ], and their families, advances in the understanding and treatment of pain can make a real difference. Seeing her husband’s pain under control made his illness more bearable for her and for the couple’s children, said [ ] “When there was no pain, or less pain, he was able to eat; he was able to have conversations; he was able to watch the TV. It’s hard to see somebody in pain, especially somebody that you love,” she said. “It’s very hard.” Lifting that burden from patients and their families is the greatest benefit of effective pain management.

For more information, contact Dr. Bruera at (713) 792-6084, Dr. Cleeland at (713) 745-3470, or Dr. Burton at (713) 745-7246.
2000 annual meeting of the American Society of Clinical Oncology, physicians asked 51% of patients younger than 65 to participate in clinical trials but only 35% of patients over 65. In most cases, physician bias stems from the assumption that older people cannot withstand cancer treatment or that the risk and discomfort of certain treatments are not worth the benefits.

"But unless you ask the question, you don't really know that, do you?" said Dr. Zwelling. "The place where you want to include older people is in the trial so that you can begin to establish if there are significant differences between the way they respond and the way younger patients respond."

**Better criteria**

Performance status—which takes into account level of activity, ambulation, and ability to care for oneself—and the presence of comorbid conditions that may be exacerbated by the treatment are more reliable criteria for clinical trial eligibility than age.

"If you have a 50-year-old with coronary artery disease and renal failure, he has a far greater risk of toxicities from drugs than would an 80-year-old who is physiologically fine, who has a good performance status," Dr. Zwelling said.

It is true, however, that in general older people are more likely to have comorbid conditions and a poorer performance status. The most common comorbid conditions that could make patients ineligible for a clinical trial are hypertension, diabetes, and vascular disease. Reduced kidney, liver, or lung function can also preclude certain treatments. However, a history of comorbid conditions alone should not prevent someone from entering a trial, provided that the condition has been well controlled.

"Just because you have [a comorbid condition] does not mean you won't be able to get treatment. However, if it is poorly controlled and you have complications related to it, then it could affect your ability to get treatment," said Mary Ann Weiser, M.D., Ph.D., an associate professor in the Department of General Internal Medicine, Ambulatory Treatment, and Emergency Care. "But again, it doesn't have to do with age. If someone is 90, and they don't have any other medical problems, and they get a cancer, if they want to be treated for it—even though, maybe, the treatment is not going to cure them and it is going to make them sick—if they want to try it, I think that they should be given the option."

A study published in April 2003 in the *Journal of Clinical Oncology* casts doubt on the practice of the wholesale use of comorbid conditions as exclusion criteria in clinical trials. The study found that such protocol exclusions account for almost all of the underrepresentation of older people in cancer clinical trials. Fewer older people were enrolled in trials that excluded patients with high blood pressure; other heart, lung, or blood abnormalities; or limitations on their ability to perform daily living functions without help. The researchers recommended that protocol exclusions be based solely on the specific toxicity of the regimen.

"Hopefully, [a researcher's] comorbid exclusions are chosen for a reason," said Dr. Zwelling. "You're not just sort of plucking them off a shelf. In a phase I trial, it should be linked to what you see in animals. After that, you should have enough information from humans to know what the drug is likely to do and what its toxicity is likely to be."

**The effects of aging**

While age alone should never make a patient ineligible for a trial or other treatment, the effects of aging on bodily (Continued on page 6)
Participation of Elderly Patients in Clinical Trials

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functions and physiology cannot be ignored when making treatment and referral decisions. Pharmacokinetic processes such as the absorption, metabolism, and excretion of drugs appear to be different in older patients, and in general, a person’s physiologic tolerance or reserve diminishes with increasing age.

“The process of aging reduces your organ capacitance,” said Michael Fisch, M.D., an assistant professor in the Department of Palliative Care and Rehabilitation Medicine. “You may have a functioning kidney, functioning lungs, and a functioning brain, but you have less capacitance than you did 20 years ago when you were 50. ... Older people are generally closer to some edge beyond which they would tip into a more clinically important organ dysfunction. But that doesn’t mean that you can’t set the same goals for treating and controlling their disease. To me, age bias means that you put unreasonable limits on your expectations for a person because they’re 80—as if two years of life between 80 and 82 are not as valuable as two years of life between 50 and 52.”

Dr. Fisch added that decisions about the care of older patients with cancer must take into account the stage and type of cancer and the patient’s competing risks. “If you are 82 and you have lots of other diseases, if you have early-stage prostate cancer, it is not likely to catch up with you,” he said. “That is not age bias; it is just making appropriate medical decisions in the face of competing risks and the expected course of illness. But what people often don’t realize is that if you check the life expectancy tables, a healthy 82-year-old man would be expected to live six years. And so if you are caring for a person that has a disease that is expected to catch up with them in 18 months, then you’d better worry about that disease.”

Opening the doors

In June of 2000, a major barrier to elderly patients’ participation in clinical trials was lifted when the U.S. government announced that Medicare would begin paying patient care costs for individuals enrolled in clinical trials.

The NCI announced in the fall of 2003 the launch of a new initiative to accelerate the study of cancer and aging. The five-year, $25-million grant program has identified seven areas for study: patterns of care; treatment efficacy and tolerance; effects of comorbidity on cancer treatment; prevention, risk assessment, and screening; psychosocial issues and medical effects of treatment; palliative care, end-of-life care, and pain relief; and the biology of aging and cancer.

Some research suggests that older people are less likely to participate in clinical trials, even when invited, and prefer to be cared for by a community physician rather than in a specialty cancer center. One possible reason is that frequent follow-up visits may be difficult for older people living alone.

“Maybe it is true that patients older than 80 are underrepresented in clinical trials because access to medical centers is more difficult,” said Luis Fayad, M.D., an assistant professor in the Department of Lymphoma. However, Dr. Fayad said, “Are elderly patients more reluctant to participate in clinical trials? No, I don’t think so. I think they have a very open mind about trials.”

Dr. Fayad added that many older people are willing to participate in clinical trials for the sake of advancing scientific knowledge, even if they are unlikely to personally benefit from their participation. Such altruistic motivations are one of the many variables that should be considered when offering clinical trials to elderly patients. Above all, said Dr. Fisch, the person discussing clinical trial enrollment with the patient should be someone with whom the patient already has a trusting, ongoing relationship. “To go on a clinical trial, you have to really understand how the whole thing fits in—who is responsible for you and what your treatment will be,” Dr. Fisch said. “And when they find that and when the trials are put into the proper context, elderly patients are very likely to go on trials. They are as likely as anybody to go on trials.

“Older adults want the same things as everybody else. They want to live; they want to get treatment; they want to have their dignity preserved. Overwhelmingly, people have some meaning and purpose in their lives that motivate them to strive to live as long and as well as possible.”

FOR MORE INFORMATION, contact Dr. Zwelling at (713) 794-4500, Dr. Weiser at (713) 745-4516, Dr. Fisch at (713) 792-3936, or Dr. Fayad at (713) 792-2860.
From Cancer Research to Clinical Practice

New information emerges every day on cancer prevention, diagnosis, and treatment. How is this information discovered, and how are new findings translated into clinical practice? The following is a very brief overview of the journey from the cancer research laboratory to the clinic.

Funding
To obtain funding for their research, physicians and scientists apply for grants from government agencies (such as the National Cancer Institute) and private organizations (such as the American Cancer Society). Grant applications detail what the researcher proposes to do and why the proposed research is important. Applications are evaluated carefully by panels of scientists with expert knowledge of the subject. Only the most promising projects are funded, and researchers who receive funding are required to submit progress reports to demonstrate that they are using the funds wisely.

Research
Cancer research can be broadly divided into three categories: basic science studies, which are conducted in laboratories; animal studies; and clinical studies, which are conducted in people.

Some clinical studies are clinical trials, which test new prevention, diagnosis, or treatment strategies to determine whether they are safe and effective. Before physicians can conduct a clinical trial, they must obtain approval from an oversight committee known as an institutional review board, which ensures that the study will provide important information and that the risks it involves are reasonable and are explained carefully to participants.

In other clinical studies, researchers review medical records from patients to answer important questions. For example, in a recent study, researchers reviewed records to learn how many extra cancers would develop if cervical cancer screening were performed every three years instead of yearly.

Communicating new findings
When researchers complete a study, they report their findings in a journal article. Journal articles serve as news releases to the medical and scientific communities. Journal articles have five standard parts: an Introduction that tells why the study was done, a Methods section that explains how the study was conducted, a Results section that details the findings, a Discussion in which the authors describe what the findings mean, and an Abstract, a brief summary of the entire report.

Before a report is published, it must pass through a rigorous quality-control process called peer review. The journal sends the report to scientist and physician volunteers with expert knowledge of the topic. They scrutinize the report to determine whether it adds important new information and whether the data presented support the authors’ conclusions. To ensure objective evaluation, reviewers’ identities are not shared with a report’s authors and vice versa. In most cases, authors have to revise their paper before it is accepted for publication.

Researchers constantly scan journals in their fields to keep up with new developments and seek ideas for future research.

Incorporating findings into clinical practice
It would be wonderful if every clinical study led to a definitive answer; for example, “drug A is better than drug B for treating prostate cancer.” In the real world, however, all findings are associated with a degree of uncertainty. Rarely does one study by itself lead to a change in clinical practice. More often, evidence from multiple studies accumulates over time, and eventually a consensus is reached. In the meantime, there may be spirited debates in the medical community about which approach is better. The controversy over mammography screening in women 40 to 49 years of age is a case in point—some experts think that screening in this group is warranted, but others do not.

The landscape of knowledge about cancer is constantly shifting; as soon as researchers get their bearings in one region, the geography of another region changes. New findings are constantly being reported that suggest new and better patient-care approaches, triggering further research and a new search for consensus. This fast-changing research environment reflects physicians’ and scientists’ main desire: to find as quickly as possible the best approaches for people affected by cancer.

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

(800) 392-1611, Option 3, within the United States, or
(713) 792-3245 in Houston and outside the United States.

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The Next 20 Years: The Changing Face of Cancer Treatment

Emil J Freireich, M.D.
Director, Adult Leukemia Research Program

Fifty years ago, there was no effective treatment for systemic or metastatic cancer. Since then, systemic treatments have been developed that can cure at least 10% of these patients. The first cures were for choriocarcinoma, a highly malignant neoplasm of the placenta. This was soon followed by the discovery that combination chemotherapy was curative for the majority of children with acute lymphoblastic leukemia, patients with Hodgkin’s disease, and patients with testicular cancers. Curative therapy has also been discovered for a minority of patients with adult acute leukemia, large cell lymphoma, and other pediatric neoplasms.

The dramatic discovery and licensing of the drug Gleevec has revolutionized research on cancer treatment. The story of its development is exciting and important. The discovery of a specific chromosomal abnormality, the Philadelphia chromosome, characterizing chronic granulocytic leukemia, led to the isolation of a unique gene, the BCR/ABL gene, which is translated into a unique protein, the BCR/ABL protein. This protein could be isolated, purified, and crystallized and its secondary structure described. Identifying the active site of this catalytic protein allowed the design of small molecules that bind specifically to this site, thus inactivating the protein. The small molecules were tested against the specific protein by using high-throughput screening, that is, screening thousands of compounds to identify the most effective inhibitory molecule. This molecule moved quickly into clinical trials in patients with chronic granulocytic leukemia, for whom the average survival time was less than three years, and has totally transformed this disease, which is now virtually controlled, with a more than 95% five-year survival rate. Although it is not certain that patients can be cured with Gleevec alone, the administration of these pills can convert a highly lethal form of cancer into a chronic illness, analogous to the way HIV drugs control AIDS.

Moreover, this small molecule can inhibit other proteins, specifically a mutated KIT protein in gastrointestinal stromal tumors, which are highly resistant to chemotherapy yet respond dramatically to the oral administration of Gleevec. This example further encourages the pursuit of small molecules to control the common malignancies of the colon, lung, breast, and prostate, for which chemotherapy has only palliative benefit.

The next 20 years will see a revolution in cancer therapy based on the discovery and development of small molecules targeted to specific proteins in the cell that are necessary for the proliferation and survival of the cancer cells within the host. I feel confident that these advances will convert metastatic systemic cancers into chronic illnesses, which can be suppressed and managed for many years.