For most people, fever is not an emergency, and there would be no need for immediate care. But for cancer patients, who often have compromised immune systems, it's a much different story. Neutropenic fever can signal the development of a

(Continued on next page)
Emergency Care for Cancer Patients
(Continued from page 1)

serious and fast-acting bacterial or fungal infection that requires immediate and aggressive treatment. This patient should go to the nearest emergency room.

“In fact, even if this were one of our patients, she would be instructed to go to the nearest emergency room if she was more than 30 minutes away, rather than drive farther to come here,” said Cecil Brewer, clinical administrative director of the Emergency Department at The University of Texas M. D. Anderson Cancer Center. And while he concedes that most cancer patients would prefer to be treated where their cancer and cancer treatment are known, that’s not always possible.

Reasons for ER visits

Many cancer patients need some type of emergency care during the course of their illness and treatment. Neutropenic fever is one of the most common reasons, but there are a number of others as well. Oncologic emergencies are usually either compressive/obstructive, metabolic, or cytopenic in nature:

• Obstructive or compressive complications can arise when tumors—either primary or metastatic—impinge on nearby organs or structures. Brain tumors or metastases can cause seizures, headaches, strokes, and a host of neurologic symptoms, for example. Spinal cord compression, deep vein thrombosis and pulmonary emboli, superior vena cava syndrome, and obstructed ureters, vessels, airways, and ducts are other examples of compressive or obstructive conditions. Some of these conditions—pleural and pericardial effusions and cardiac tamponade, for example—can result either from the cancer itself or from treatment effects, notably radiation.

• Metabolic emergencies like hyperuricemia and hypercalcemia can arise when tumors secrete hormone-like peptides that can disrupt electrolyte balances. Tumor lysis syndrome is a metabolic crisis caused by the destruction of cancer cells. As neoplastic cells die in response to therapy, their intracellular contents are spilled into circulation, causing hyperuricemia and potentially severe disturbances in all of the major electrolytes.

• Cytopenic crises in cancer patients who present for emergency care include thrombocytopenic bleeding, neutropenic fever, and acute autoimmune hemolytic anemia. Of these, neutropenic fever is the most common and is usually related to the immunosuppressive effects of chemotherapy, which render patients highly susceptible to potentially dangerous infections.

M. D. Anderson’s Emergency Center (EC) saw about 19,000 patients last year. Most were M. D. Anderson patients. About 86% of them presented with urgent or emergent conditions.
The care given in a cancer center EC is more holistic than single-problem oriented care and is thus labor and resource intensive.

Not all were directly related to cancer; the focus of this facility is not limited to “oncologic emergencies” but rather to any urgent care needs of cancer patients.

“Cancer patients are not immune to the things that send other people to emergency rooms, too; incidents arising from co-morbidities, such as heart disease or diabetes, are common. In these cases, cancer may be a complicating backdrop, increasing the complexity of the situation,” said Margaret B. Row, M.D., who is medical director of the Emergency Center and section chief of Emergency Care at M. D. Anderson.

Uniquely, the EC in this cancer center is staffed by non-oncologists like Dr. Row—physicians whose first specialties are internal or emergency medicine but who now specialize in the emergency care of cancer patients. Dr. Row notes that one of the professional rewards of this unique subspecialty of emergency medicine is that the staff develops long-term relationships with patients, which is not usually the case for emergency personnel.

A specialized Emergency Center

Compared with a conventional emergency room, there are other differences: no burns, obstetrics, or trauma, of course. Few cases can be processed quickly. Quite often, for example, a patient presenting to a conventional ER with a fracture can be transferred directly to an orthopedic department: x-ray—cast—discharge. A cancer patient with a fracture—possibly a pathologic fracture—is a different story. The workup and evaluation is not a fast process in this setting, and patients are admitted to inpatient care—including ICU—more often than they are from a conventional ER.

The care given in a cancer center EC is more holistic than single-problem oriented care and is thus labor and resource intensive. But the cancer center EC makes sense for cancer patients, who often feel more secure about treatment—even for other conditions—in a facility where their cancer is understood. It is unique, and the demand for its services is growing.

“We are seeing increasing numbers of patients, and as treatments become more aggressive, we often see sicker patients,” noted Mr. Brewer. To better meet the growing needs, construction of a new EC facility is underway at M. D. Anderson; it will have increased space and bed capacity, special procedure rooms, a unit designed for fast-track cases, and one for 24-hour observation, and it will be located in convenient proximity to imaging and other important services. There will be easy access for automobiles and ambulances, and there will be a 24-hour dedicated pharmacy and diagnostic imaging and laboratory services. “Concurrently we’re implementing high-tech patient tracking and other workflow efficiencies,” said Mr. Brewer, noting that medical and nursing staff have been very involved in the design of the new unit. “It will be one-of-a-kind,” he said.

Starting with “What would the perfect ER setting be?” Dr. Row said that medical and nursing staff worked with designers and architects on the plan and made site visits to other facilities. The new facility will be uniquely tailored not just for emergency medical care but also for the unique needs of cancer patients: the new plan involves patient advocacy, case management, and food services; the single rooms are designed to provide privacy and comfort for patients and their families as well as protection from infection.

Resource for local physicians

But not all cancer patients who need emergency care will be treated at a facility like this. M. D. Anderson and Memorial Sloan-Kettering are the only comprehensive cancer centers in the United States that offer this highly specialized service.

Most cancer patients who need emergency care will receive it in their local emergency department, so the EC staff at M. D. Anderson is also committed to helping support their colleagues elsewhere. Toward that end, M. D. Anderson recently hosted the second annual “Oncologic Emergencies” conference for community health care providers in internal and emergency medicine as well as oncology. An additional resource is Oncologic Emergencies (B.C. Decker, 2002) by M. D. Anderson physicians Sai-Ching Jim Yeung, M.D., Ph.D. and Carmen P. Escalante, M.D. that is written for community physicians and emergency physicians who may not see oncology patients on a regular basis.

And finally, M. D. Anderson’s EC staff consults with physicians at other facilities by telephone about a cancer patient’s care. “We are often a resource for the emergency physician elsewhere who must cover a much broader range of conditions and is now confronted with a cancer emergency,” said Mr. Brewer.

“Sometimes,” added Dr. Row, “that is just a medical discussion, but there are other times it may mean helping colleagues in other ways, such as assisting them with difficult conversations with families, or offering the kinds of emotional support we have found that cancer patients need in these situations.”

FOR MORE INFORMATION, call (713) 745-4516.
Bringing Clinical Trials to the Community

Access to a national network of the most current clinical trials may be closer than you think, thanks to the Community Clinical Oncology Program.

by Ellen McDonald, Ph.D.

Even if your practice is hundreds of miles away from a university hospital or cancer center, your cancer patients can still have the opportunity to participate in cutting-edge clinical trials close to home, thanks to the National Cancer Institute’s (NCI) Community Clinical Oncology Program (CCOP).

CCOP was conceived over 20 years ago as a way to make the most promising clinical trials accessible to more people throughout the country. Most of the top, federally sponsored research programs are at major cancer centers or in regional cooperative groups, but most cancer patients are treated by local oncologists or primary care physicians. This program brings the two together, linking more than 4,000 community practitioners to cancer research initiatives in a network of CCOP research bases around the country. The University of Texas M. D. Anderson Cancer Center is one such research base.

The NCI funds and trains local and regional physician groups and hospitals that serve as CCOP sites, as well as the cancer centers or cooperative groups conducting the studies and serving as research bases. Each of the 63 CCOP sites is allied with several research bases—typically, with two to three cooperative groups (e.g., the Southwest Oncology Group) and one or two cancer centers.

For the physician in private practice, this means access to a national network of cancer clinical trials that are ultimately funded and overseen by the National Cancer Institute and administered by leading research centers like M. D. Anderson. Without traveling far from home, their patients may be able to take part in trials of new treatments, symptom control, or cancer prevention interventions available at the nearest CCOP site.

Ideas for trials that are conducted through the CCOP program originate from faculty and physicians at the research base as well as from physicians at local CCOP sites. Symptom control and prevention studies are ideal.

“Getting a trial approved for the program is a bit like negotiating a treaty,” said Michael J. Fisch, M.D., the medical director of the CCOP Research Base at M. D. Anderson Cancer Center. “We first suggest the concept, the gist of what we plan to do, and if the NCI approves the idea, we then supply a detailed protocol. After NCI approval, our own institutional review board has to approve the proposed study. The CCOP sites we’ll be working with also participate in the development of the study, as well as industry sponsors who will supply the new agent or product under investigation. And exactly how one brings all these people together in the process and in what order, well, there’s a bit of an art to that.”

Since it was first funded in 1987, the M. D. Anderson Cancer Center CCOP Research Base has managed 150 CCOP-associated clinical trials involving more than 5,000 patients. It is affiliated with 24 general CCOP sites and two minority-based sites.

Part of the program’s success is due to recent trends in cancer management. “In recent years, cancer care has moved a lot more toward outpatient care,” Dr. Fisch observed. “For example, many of the new molecularly targeted therapies are oral therapies that can be administered easily on an outpatient basis. Therefore, the possibility of doing research with patients in their own communities has become much more feasible, and institutions such as M. D. Anderson are increasingly turning outward in their research thinking.”

Whatever the benefits of participating in clinical trials offered by CCOP, they are of little use if community physicians and the general public are reluctant to enroll. Therefore, making the community more aware of the state of cancer research in general and of the advantages of participating in clinical trials in particular is one of the goals of the national CCOP program.

“We want people to realize that being in a CCOP clinical trial means they will receive first-class medical treatment,” – Dr. Michael Fisch
noted Dr. Fisch. “You couldn’t get better quality medical treatment than to be in a trial sponsored by the NCI. Sometimes people fear being used as ‘guinea pigs’ in experiments, but it’s not like that. Patients enrolled in these trials always get at least the best treatment available, and some, if not all, will also get the new intervention being tested. Patient care in the context of clinical trials is very closely monitored: it’s as careful as it gets.”

Besides the advantages offered to patients who would not otherwise have easy access to clinical trials, CCOP also provides a clear advantage to those conducting the studies. “If we at M. D. Anderson hit upon what we think is a promising new treatment, CCOP provides a mechanism for us to do larger studies and see if our findings hold true for patients in the community,” explained Charles Lu, M.D., an associate professor in the Department of Thoracic/Head and Neck Medical Oncology at M. D. Anderson. Dr. Lu is currently conducting a phase III study in patients with locally advanced, unresectable non-small cell lung cancer through the institution’s CCOP Research Base. “For single-center studies, especially those at a specialized cancer center, the patient population may be highly select and not representative of the general population. CCOP allows us to take our idea to the next level and see if our findings can be generalized in another, larger patient population. That’s very valuable.”

There are also benefits for the CCOP sites. “I see the main advantage of being a CCOP site as the opportunity to participate in cutting-edge science and improve cancer care,” said Peggy Verrill, Administrator of the Central Illinois CCOP. “Also, in my experience, patients are relieved to find that they don’t have to travel long distances to participate in the most current studies available.”

Most of the major successes of the NCI’s community oncology program thus far have involved cancer prevention studies whose findings have since changed standard practice. For example, few people had heard of tamoxifen before 1998, when the Breast Cancer Prevention Trial showed 45% fewer breast cancer diagnoses in women at increased risk for the disease who took tamoxifen for chemoprevention. Likewise, results from the Colorectal Adenoma Prevention Study reported in 2002 showed that daily aspirin use in patients with a totally resected early-stage colorectal cancer reduced subsequent adenoma development compared with placebo. Additionally, in 2003, the Prostate Cancer Prevention Trial showed that finasteride reduced the risk of prostate cancer in healthy men age 55 or older.

Open CCOP protocols available through the M. D. Anderson CCOP Research Base include:

**Control Trials**

- MDA 2005-0328 (MDA CCC 03-26): A Multi-Center Phase III Placebo-Controlled Trial of Celecoxib for Prevention of Capecitabine-Induced Palmar/Plantar (Hand/Foot) Syndrome in Patients with Metastatic Breast and Colorectal Cancer

- MDA 2004-0024 (MDACC CCC-01-06): Chemotherapy and Mindfulness Relaxation: A Randomized Trial at M. D. Anderson Cancer Center at M.D. Anderson Community Clinical Oncology Program

- MDA 2003-0789 (MDA CCC 02-23): Phase II Trial of Subcutaneous Amifostine for Reversal of Persistent Paclitaxel-Induced Peripheral Neuropathy

**Treatment Trials**

- MDA 2004-0727 (NCI #6810): Phase II Trial of Capecitabine (Xeloda®) and Pegylated Interferon Alfa2a (Pegasys®) for Recurrent or Progressive Brain Metastasis from Breast Carcinoma

- MDA 2004-0662 (NCI #6636): A Randomized, Factorial-Design, Phase II Trial of Temozolomide Alone and in Combination with Possible Permutations of Thalidomide, Isotretinoin, and/or Celecoxib as Post-Radiation Adjuvant Therapy of Glioblastoma Multiforme

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- MDA 2004-0342 (NCI #6484): Randomized Phase II Trial of Idarubicin and Ara-C +/- Bevacizumab in Patients Age <60 with Untreated Acute Myeloid Leukemia

- MDA 2004-0305 (NCI #6485): A Phase II Study of Rituximab-CHOP with Pegylated Liposomal Doxorubicin in Patients Older than 60 Years of Age with Untreated Aggressive B-Cell Non-Hodgkin’s Lymphoma

- MDA 2003-0922 (NCI #6459): A Randomized Phase II Study of Bone-Targeted Therapy in Metastatic Androgen-Dependent Prostate Cancer

- MDA 2003-1007 (NCI #6384): A Phase II Study of EMD 121974 as Maintenance Therapy for Patients with Acute Myeloid Leukemia in Complete Remission

- ID00-156 (MDA-3410): A Prospective Randomized Phase III Trial Comparing Consolidation Therapy with or without Strontium-89 Following Induction Chemotherapy in Androgen-Independent Prostate Cancer


**TO FIND OUT ABOUT**

Community Clinical Oncology Program sites in your region, or to inquire about the protocols listed here, call the M. D. Anderson CCOP Research Base at (713) 563-0276 or email mdaccop@mdanderson.org.

These headline-making trials were available to patients at CCOP locations throughout the country, allowing them to reap the benefits of participating in the latest clinical trials in their own hometowns—and the rewards of having access to these new treatments now proven successful, before they became standard therapy.
New Agent Effective in Gleevec-Resistant Leukemia

The targeted agent AMN107 can produce dramatic benefits in patients with some forms of leukemia that are resistant to imatinib (Gleevec), the standard therapy for these cancers, say researchers at M. D. Anderson.

Investigators have reported marked improvement in outcome in all three phases of chronic myeloid leukemia (CML) as well as benefit in treating a form of acute lymphocytic leukemia (ALL) that shares the same genetic abnormality as CML, the Philadelphia chromosome.

In a phase I clinical trial, 119 patients who were resistant to Gleevec were given AMN107. The researchers found that the range of response varied depending on the form of the cancer and the presence of genetic mutations. For example, hematologic response from the drug (defined as control of white blood cell counts) ranged from 44% to 100% in different subgroups of CML patients, and the more enduring cytogenetic response (elimination of cells with the cancer-causing defect) ranged from 22% to 100%. There was less overall response in ALL patients (ranging from 10% to 33%, depending on extent of disease).

“$\text{This drug is very promising and appears at this point to offer an effective option for patients who do not achieve an optimal response to Gleevec therapy,}$” said Hagop Kantarjian, M.D., professor and chair of the Department of Leukemia and principle investigator for the study. He says the results suggest that physicians soon will be able to tailor leukemia therapy according to the molecular profile of the disease, offering different treatments for subsets of patients based on their cancer’s distinct molecular signature.

If additional studies continue to show such results, Dr. Kantarjian believes AMN107, which is taken in pill form, “will either replace Gleevec as the standard of care in the future or will be used in combination with it.”

Immune Cell Key to Inflammatory Diseases

The molecular roots of inflammatory and autoimmune diseases such as asthma, arthritis, and multiple sclerosis have been discovered by a team of researchers led by M. D. Anderson Cancer Center. They say their findings may point to ways to effectively treat these diseases—if not stop them before they start.

In a lead article in the November 2005 issue of Nature Immunology, the scientists report finding a novel type of “T helper” cell they say is the culprit for initiating chronic inflammation and autoimmunity in a variety of body tissues. This newly described T cell—which they call an inflammatory TH cell (or THi)—produces interleukin 17 (IL-17), a potent cytokine that researchers have already linked to an immune system gone awry.

“We suspected that IL-17 is a player in autoimmune and inflammatory diseases, but we didn’t understand where IL-17 came from before this finding,” said the study’s lead investigator, Chen Dong, Ph.D., an associate professor in the Department of Immunology.

“Now we have discovered the source of IL-17 and also have solidly demonstrated that these are the crucial cells that regulate tissue inflammation in autoimmune disease and asthma,” he said. “These findings suggest that shutting down the activity of these THi cells might stop chronic inflammatory diseases from developing in the first place.”

He adds that while such drugs are years away from development and clinical trials, agents that block IL-17 could represent an effective treatment, based on these results.

While the findings have no immediate relevance to the field of oncology, it is known that cancer can arise from inflammatory processes. Further understanding of how the immune system functions, and how it can go awry, is important, Dr. Dong said.

Factors Behind the Decline in Breast Cancer Deaths

Early detection through screening mammography and improved adjuvant treatment have contributed almost equally to the substantial decrease in breast cancer death rates over the past 10 to 15 years, researchers concluded in an unprecedented effort to parse out the factors that have led to the decline.

The study, published in the October 27, 2005, issue of the New England Journal of Medicine, was supported by the National Cancer Institute and conducted by seven research groups, including M. D. Anderson Cancer Center.

Researchers sought to end the longstanding controversy of whether screening mammography, better treatment, or a combination of the two is responsible for improved breast cancer survival.

Seven research teams reached somewhat different conclusions but were closest to each other in estimating how much the adjuvant therapies tamoxifen and chemotherapy reduced mortality in patients (12% to 21%, with a median of 19%). The range for screening mammography, however, was 7% to 23% (with a median of 15%), reflecting the greater uncertainty associated with estimating the benefit of screening.

Still, according to the models, the combination of screening and adjuvant therapy reduced the breast cancer death rate by an estimated 25% to 38%, with a median of 30%—which explains the drop in breast cancer mortality from 1975 to 2000, said the study’s lead author, Donald Berry, Ph.D., chair of the Department of Biostatistics and Applied Mathematics at M. D. Anderson.

“While we didn’t agree with each other as to the percentages of benefit, all seven groups concluded that the decline in the rate of death from breast cancer is a combination of screening and therapy and not restricted to one or the other,” he said.
The immune system is a complex network of cells and chemicals that forms the body’s defense against foreign invaders. Researchers in the relatively young field of cancer immunology are harnessing the power of this defense system to seek out, destroy, and even prevent cancers.

How the system works

The immune system, like any organization, has members that perform different jobs to accomplish a common goal. In this case, the goal is to recognize foreign invaders—including bacteria, viruses, parasites, and even cells from other people—destroy them, and remember them in case of later attacks.

Some immune cells recognize chemical signals given off by common bacteria and other foreign invaders and quickly mobilize to destroy them by swallowing and dismantling the foreign material or releasing chemicals that break it down. Other immune cells can adapt to protect the body against specific attackers by producing molecules called “antibodies” that attach to specific bits of proteins, or “antigens,” that are displayed on the surfaces of cells and viruses, tagging them for destruction by other immune cells.

The immune cells orchestrate their efforts and communicate with each other and with other cells of the body through cytokines and growth factors, which are chemical “messengers” produced by one cell that alter another cell’s behavior.

What goes wrong in cancer?

Every cell in your body displays antigens on its surface, but your immune cells are trained to recognize these “self” antigens and leave those cells alone. This is the problem with cancer, however: the body’s own cells multiply out of control, but the immune system is generally blind to it because it recognizes the tumor cells as being “self.”

Cancers can’t always hide from the immune system. The same genetic mutations that cause cancer cells to multiply wildly and become responsive to growth factors can also change the proteins on the tumor cells’ surface, resulting in “tumor antigens” that are no longer recognized as “self” by patrolling immune cells.

Unfortunately, this “immune surveillance” doesn’t always work. As the tumor cells multiply, their genes continue to mutate, and the surface proteins can change so fast that the immune system can’t keep up with recognizing all the tumor antigens. Immune surveillance can also break down if the immune system is overwhelmed by stresses like chemotherapy or diseases like AIDS. Cancer-causing viruses can also trick the immune system by lying low within infected cells even as they take over the cells’ machinery and cause them to multiply abnormally.

Using immunotherapy to fight cancer

Researchers are now working on ways to harness the immune system’s many talents and turn them against tumors. These types of cancer treatments are collectively known as immunotherapy.

One such tactic involves designing antibodies that recognize specific tumor antigens. These antibodies can be used to tag cancer cells for destruction by immune cells, to slow the growth of cancer cells by preventing them from using the body’s growth factors, or to send lethal chemotherapy drugs or radiation directly to the tumor cells without affecting the surrounding normal cells.

Some immunotherapies take advantage of the body’s naturally occurring cytokines and growth factors. Some of these molecules can improve the way the immune system fights cancer—by stimulating the growth and activity of various immune cells—or they can directly slow the growth of cancer cells down to a more normal level. Other molecules can protect the body from the harmful side effects of chemotherapy, allowing doctors to give patients a higher dose of the drugs.

Other immunotherapies that are currently being tested involve “educating” the immune system to better recognize tumors. Cancer vaccines, for example, flood the immune system with tumor antigens to mobilize immune cells against the tumor. In addition to slowing a tumor’s growth or destroying it, vaccines could potentially be used to prevent tumors from recurring or prevent healthy people from developing cancers in the first place.

The field of cancer immunotherapy holds a great deal of promise, but it is still in its infancy and many unanswered questions remain. For information on current clinical trials in immunotherapy, visit the National Cancer Institute’s clinical trials website at www.cancer.gov/clinicaltrials/. The NCI’s Understanding Cancer Series also has a slideshow with more detailed information about the immune system (www.cancer.gov/cancertopics/understandingcancer/immunesystem).
Cognitive Dysfunction in Cancer

Christina Meyers, Ph.D.
Professor and Chief, Section of Neuropsychology

Cancer patients experience a number of adverse symptoms that affect the quality of their lives, including cognitive impairment, fatigue, pain, sleep disturbance, and others. Cancer treatment is only truly successful if these symptoms are managed, but successful management can be hampered by insufficient knowledge of mechanisms or a lack of awareness of the problem.

Cognitive dysfunction occurs in the majority of cancer patients on active therapy and is not infrequently a symptom that heralds the diagnosis. It persists in many patients long after treatment is discontinued. Popularly termed “chemobrain” or “chemofog,” the cognitive impairment can actually be due to factors besides chemotherapy, including the disease itself.

Cancer patients with cognitive dysfunction often present with complaints of memory disturbance. These problems may not be clinically obvious but become evident in neuropsychological testing, particularly in relation to the individual’s pre-illness level of function.

In these patients, objective testing of memory generally demonstrates a restriction of working memory capacity (e.g., the person is able to learn less information, and learning may be less efficient), and inefficient memory retrieval (e.g., spontaneous recall may be somewhat spotty). However, the ability to store new information is generally intact, meaning that the memory disturbance in cancer patients is vastly different from that in neurodegenerative disorders such as Alzheimer’s disease.

Additional common symptoms of cognitive impairment in cancer patients include periodic lapses of attention, distractibility, and slowed cognitive processing speed. In general, reasoning and intellectual functions are not affected, but patients often have difficulty performing their normal work due to cognitive inefficiencies.

The effect of these symptoms on daily life can be quite profound, depending upon the demands of the individual’s work and home life. Many patients observe that they can no longer multi-task and that they may become overwhelmed when too much is happening at once. They tend to be easily distracted and may go from project to project without completing them.

Finally, many patients note that it takes increased mental effort to perform even routine tasks. This contributes to the fatigue that is often a co-existing symptom. In fact, cognitive impairment generally does not occur in isolation, but interacts in a negative way with fatigue, pain, sleep disturbance, and depression. Unfortunately, these distressing symptoms frequently go under recognized and untreated.

New intervention strategies are being developed to improve patient function and quality of life—for instance, recent studies have shown the drug methylphenidate (Ritalin) to be an effective tool in treating cognitive function problems. Optimizing the quality of life of cancer patients is possible, essential, and should be on equal footing with antineoplastic therapy.