Medical problems that may seem routine in patients without cancer often mean something different or have a different cause in cancer patients and may be much more serious, requiring urgent treatment. Managing these problems promptly and effectively is a challenge faced by all cancer centers.

The University of Texas MD Anderson Cancer Center has a unique solution: its own dedicated emergency department (ED), also known as the Emergency Center. “We have the only true ED in the nation dedicated solely to cancer patients,” said Terry Rice, M.D., an assistant professor in the Department of Emergency Medicine and medical director of the Emergency Center.

In addition to classic oncologic emergencies, cancer patients may experience a broad spectrum of medical problems related to their cancer. “Even nonspecific symptoms such as lethargy, confusion, nausea, or fever require special attention in a patient with cancer,” Dr. Rice said. Awareness of common problems that can lead to emergencies in cancer patients helps ED physicians provide prompt and appropriate care.

Common oncologic emergencies

Classic oncologic emergencies are usually categorized according to their cause: the cancer treatment or the underlying disease. Emergencies resulting from the cancer itself include life-threatening metabolic abnormalities such as severe electrolyte imbalances; organ insufficiency; and hematological abnormalities such as leukostasis, hyperviscosity syndrome, and symptomatic cytopenias. Other disease-related
Emergency Care for Cancer Patients
[Continued from page 1]

oncologic emergencies include complications of solid tumor progression, such as mass effects in the brain or spinal cord or organ failure due to invasion or obstruction. Treatment-related emergencies include chemotherapy-induced nausea and vomiting, diarrhea, fever in neutropenic patients, mucositis, and graft-versus-host disease.

In a broader sense, however, any urgent problem that is potentially more severe in cancer patients than in the general population might be considered an oncologic emergency. Summarized here are some of the emergencies seen most often in the MD Anderson ED.

Opportunistic infections
Current and former cancer patients are at higher risk than people without cancer for opportunistic infections, which may lead to sepsis. “Both cancer and its treatment can disrupt normal immune responses,” Dr. Rice said, “and most cancer patients, whether they are currently in treatment or are longer-term survivors, are at high risk for unusual infections that might go unrecognized in some acute care settings. The presenting symptoms may be atypical or nonspecific, such as fever, lethargy, or shortness of breath.”

Many patients seen in the MD Anderson ED have neutropenic fever, which may be related to cancer or, more often, its treatment. Current guidelines recommend that antibiotic therapy begin within 1 or 2 hours of neutropenic fever onset in cancer patients. However, these guidelines sometimes go unmet in the general medical setting owing to a lack of recognition of the neutropenia until blood test results are available and to practitioners’ general reluctance to give antibiotics without knowing the cause of a fever. Either of these reasons can cause a dangerous delay in treatment.

In cancer patients with fever or other infection-related symptoms, neutropenia should be suspected immediately. “At our ED,” Dr. Rice said, “we know from patients’ history and medical records that they are likely to be neutropenic, and we treat them very aggressively. Blood specimens are drawn immediately for culture, and appropriate antibiotic therapy is initiated without delay.”

Spinal cord compression
Back pain due to spinal cord compression, a fairly common presentation of cancer patients at conventional EDs, is also common at the MD Anderson ED. Spinal cord compression may be seen in patients with multiple myeloma or any cancer that metastasizes to the bone.

In cancer patients, spinal cord compression, often a sign of disease progression and impending neurological deficit, is a medical emergency that must be recognized and treated immediately. In any cancer patient who presents with back pain, spinal cord compression should be suspected and magnetic resonance imaging of the spine obtained immediately. Treatment consists of immediate steroid therapy to reduce swelling as well as radiation therapy or surgery to relieve the pressure on the spine.

“Neurological deficits caused by spinal cord compression often are not reversible,” Dr. Rice said. “We want to start treatment at the time the patient has pain, before the weakness or sensory loss starts.”

Neurological symptoms
Metastatic cancer to the brain often manifests as neurological symptoms. The symptoms depend on the area of the brain affected. Seizure is one of the most common and serious neurological symptoms.

Seizures in cancer patients require immediate imaging and treatment. As in patients with spinal cord compression, steroid therapy is usually begun immediately and radiation therapy started the next day. Patients with seizures resulting from brain metastases may also be assessed for gamma knife radiosurgery, which can shrink tumors and reduce symptoms.

Pain
MD Anderson patients may visit the ED with new, worsening, or breakthrough cancer-related pain. These patients often require tightly scheduled opiates and may require additional treatment for associated symptoms such as nausea, diarrhea, and dehydration.

One of the most common presentations in the ED at MD Anderson is abdominal pain. In some cases, abdominal pain is a surgical complication; in others, it is due to progressive disease. Immediate recognition and treatment of the source of the abdominal pain are essential. The source may be something as simple as constipation, but bowel obstruction or perforation is not uncommon.

“In cancer patients, bowel obstruction may be handled differently and treated in a more conservative way,” said Patricia Brock, M.D., an assistant professor in the Department of Emergency Medicine and a surgeon who has

“Increasingly, ED practitioners are going to see patients with oncologic emergencies.”
– Dr. Patricia Brock
worked in the MD Anderson ED almost 5 years. “We may not use nasogastric tubes as frequently, for example. In some cases, patients are palliated with hydration, octreotide, and steroids.”

**Nausea and vomiting**

Nausea and vomiting have many different causes and are common reasons for patient visits to healthcare practitioners. In cancer patients, however, severe nausea and vomiting may be due to the treatment or to the cancer itself. Nausea and vomiting are usually treated aggressively with antiemetic drugs such as ondansetron and steroids.

**Emergencies related to specific treatments**

Oncologic emergencies related to specific treatments vary widely. Some chemotherapy drugs can result in the reactivation of a chronic infection, such as hepatitis B, resulting in acute liver failure. Knowledge about the patient’s treatment makes it easier for ED physicians, in consultation with the patient’s oncologist, to initiate the appropriate diagnostic and therapeutic processes.

In addition, new cancer treatments can have unusual side effects. For example, the new agent ipilimumab, which stimulates the immune system, can cause life-threatening adverse effects due to the activation and proliferation of T cells. Among these effects are inflammation of the hypophyseal portion of the brain and severe diarrhea from colitis.

“In our ED,” Dr. Rice said, “we have heightened awareness of the new therapies that are being introduced and their unusual side effects.”

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### The Emergency Center: First of Its Kind

The MD Anderson Emergency Center is the only ED in the United States dedicated to cancer patients. A true ED in all senses, it operates under the ethical and legal guidelines of the U.S. Emergency Medical Treatment and Active Labor Act. “As a full-fledged ED,” Dr. Rice said, “we have all the resources needed to handle almost any emergency that a conventional ED can handle. However, our focus is on internal medicine– and surgery-related problems specific to cancer patients.” Recently, MD Anderson granted department status to the Emergency Center faculty, which made it the first academic department of emergency medicine dedicated to oncologic emergencies.

MD Anderson’s ED evolved over time. Its predecessor was an open ward staffed by nurses who would triage patients with urgent problems and call oncologists to see patients on an unscheduled basis. This not only played havoc with physician and clinic schedules but also forced patients to wait longer than necessary to receive care. As the number of patients using the facility grew, several internists were hired to staff the unit, and in 2007 the ED moved into a fully equipped and dedicated new facility.

The ED now treats about 70 patients each day. There are 45 beds plus five chairs for patients with less urgent problems. “Our length of stay is longer than that of conventional EDs, which is why we need so many beds,” Dr. Rice said. “The reason it takes so long to care for our patients in the ED is that our patients are very sick and have multiple problems; a lot of them receive fluids and blood products as well as intravenous antibiotics.” Just over half of the patients who come through the ED are admitted to the hospital, a much higher proportion than in a conventional ED.

The majority of the MD Anderson ED physicians are trained in internal medicine, which gives them a strong background in the serious metabolic and hematological problems that can occur in cancer patients. Others are trained in infectious diseases, surgery, or emergency medicine. “The diversity of physician backgrounds and training is a huge asset,” Dr. Brock said. “It enables us to draw on one another’s expertise to deliver exceptional care.”

### Non-oncologic emergencies

Although many emergencies in cancer patients are related to the cancer or its treatment, many others are not. Any medical condition, as well as its treatment, must be considered in light of a patient’s cancer. For example, a cancer patient who is being treated with an anticoagulant for stroke prevention may have bleeding problems if he or she becomes thrombocytopenic as a result of his or her cancer or its treatment.

Furthermore, cancer patients can have the same emergencies that occur in patients without cancer. “A patient with cancer also can have a myocardial infarction or appendicitis,” Dr. Brock said. “As ED physicians in a cancer center, we can’t just forget about the more common problems. We have to keep that whole list in mind as well as the lists of cancer- and treatment-related problems.”

### Education about oncologic emergencies

One of the goals of the MD Anderson ED staff is to educate community clinicians about the special kinds of medical problems that occur more often, or differently, in cancer patients. MD Anderson is sponsoring a conference in November that will help community ED physicians acquire a skill set that they can use in their own EDs to evaluate patients with oncologic emergencies.

“As the population ages,” Dr. Brock said, “cancer will be more and more prevalent. Increasingly, ED practitioners are going to see patients with oncologic emergencies. Our goal is to increase physicians’ awareness of the types of problems cancer patients and survivors may experience.”

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**FOR MORE INFORMATION**

Dr. Patricia Brock …………713-745-9911
Dr. Terry Rice …………………713-563-2098

For information about the November 13–14 conference for ED practitioners, please call 713-745-9911 or visit www.mdanderson.org/conferences.
Immunotherapy Trials Offer Hope to Patients with Metastatic Breast Cancer

By Bryan Tutt

Although the cure rate for breast cancer has risen steadily in recent decades, recurrent or metastatic disease remains difficult to control. To fight metastatic breast cancer and forestall the recurrence of high-risk primary disease, researchers at The University of Texas MD Anderson Cancer Center are using various techniques to boost the body’s immune system. Clinical trials of many of these therapies are already under way.

Recent research findings have sparked interest in the role of immunotherapy in breast cancer treatment, said Elizabeth Mittendorf, M.D., Ph.D., an associate professor in the Department of Surgical Oncology. “For a very long time, breast cancers were not thought to be immunogenic,” she said. “But data published in the past 2 years have shown that there are immune cells, including T cells, in breast tumors. This suggests that breast tumors are indeed immunogenic.”

Breakthroughs in immunotherapy against other types of cancer have encouraged research of its use against breast cancer. “The understanding of immunology in cancer is progressing very fast,” said Nuhad Ibrahim, M.D., a professor in the Department of Breast Medical Oncology. Citing the recent successes of immunotherapy drugs and vaccines in melanoma and prostate cancer, Dr. Ibrahim said, “In breast cancer we still have not had those kinds of breakthroughs, but there are definitely leads.”

Those leads have encouraged researchers to explore multiple avenues. “As much as we’ve always been fascinated with pushing the immune system, there has been no enough response to older immunotherapies, like interferon or interleukin-2, to benefit breast cancer patients,” said Debis Tripathy, M.D., a professor in and chair of the Department of Breast Medical Oncology. But with advances in therapeutic vaccines, immune checkpoint inhibitors, and other immunotherapies, he said, “We’ve finally crossed that threshold.”

Vaccines

**Anti-MUC1 vaccines**

“The early studies of immunotherapy with vaccines in patients with metastatic breast cancer did not meet their primary objective of improving overall survival, but we learned a lot from these studies,” said Dr. Ibrahim, who in the 1990s—along with James Murray III, M.D., a professor in the Department of Breast Medical Oncology—led a randomized trial of the sialyl-Tn–key-hole limpet hemocyanin (STn-KLH; also called Theratope) vaccine. The STn-KLH vaccine was derived from MUC1, a mucin expressed on the surface of a large proportion of breast cancer cells. The study did not meet its goal of extending progression-free survival for patients with metastatic breast cancer. However, in a post hoc analysis, the vaccine appeared to improve survival outcomes for patients who had previously been treated with tamoxifen (see graph on p. 5).

Dr. Ibrahim, in collaboration with the U.S. National Cancer Institute, recently completed a trial of an anti-MUC1, anti–carcinoembryonic antigen vaccine combined with costimulatory molecules and given with docetaxel. The study’s report is under peer review.

**OPT-822**

OPT-822 is a carbohydrate vaccine similar in structure to the STn-KLH vaccine. Early studies of OPT-822 demonstrated prolonged overall survival in a subset of patients with metastatic breast cancer, especially when patients received low-dose cyclophosphamide. These findings led to a multicenter trial that recently completed enrollment. Dr. Murray is MD Anderson’s principal investigator for the trial, in which patients with metastatic breast cancer received low-dose cyclophosphamide with the OPT-822 vaccine along with the lipid adjuvant OPT-821 or placebo. The results are currently being analyzed.

**E75**

Of the breast cancer vaccines, the farthest along is E75 (nelipepimut-S, NeuVax), a peptide vaccine that is derived from human epidermal growth factor receptor 2 (HER2). Dr. Murray led a small phase I clinical trial of E75 combined with granulocyte-macrophage colony-stimulating factor (GM-CSF) in patients with metastatic breast or ovarian cancer. Although HER2-specific immune responses were generated in most patients, no antitumor responses were observed, possibly because of the large tumor burden in the population studied.

“A general consensus at MD Anderson is that for vaccines to be successful

“**Triple-negative breast cancer may be a little more immunogenic than other subtypes, and that may be an opportunity.”**

– Dr. Debis Tripathy
Patients with metastatic breast cancer treated with standard chemotherapy followed by the STn-KLH vaccine who also received endocrine therapy (tamoxifen) had a longer median overall survival than did those treated with standard chemotherapy followed by a control vector. Adapted from Ibrahim NK, et al. J Cancer 2013;4:577–584.

against breast cancer, they need to be given in patients with low-volume disease, and that means giving them in the adjuvant therapy rather than the metastatic disease setting,” said Dr. Mittendorf, who also served as a principal investigator of early trials of the E75 vaccine.

Dr. Mittendorf is now the principal investigator of two multicenter trials of the E75 vaccine as adjuvant therapy for patients with HER2-positive breast cancer at high risk for recurrence: a phase III trial that has completed enrollment and a phase II trial of the vaccine plus trastuzumab that is currently enrolling patients.

**GP2 and AE37**

Two other HER2-derived peptide vaccines, GP2 and AE37, are under investigation as adjuvant therapy in an ongoing study that has completed enrollment. The GP2 vaccine—which resulted from research led by George Peoples Jr., M.D., an adjunct professor in the Department of Surgical Oncology—has greater immunogenicity than E75 and binds to both human leukocyte antigen (HLA)-A2 and HLA-A3. AE37 contains more than 10 amino acids, allowing for a broad range of immune stimulation in patients. AE37 was shown in preclinical studies to significantly enhance HER2-specific CD4-positive “helper” T cells.

Patients included in the ongoing adjuvant therapy study had a high risk for recurrence because of lymph node involvement or other factors such as high levels of HER2 expression; however, patients with HER2 immunohistochemistry scores indicating HER2-negative or borderline status were also included in the study. Because the two vaccines bind to different major histocompatibility complex class molecules, patients in the study were sorted according to their HLA status before randomization. Those who were positive for HLA-A2/A3 were randomly assigned to receive GM-CSF with or without GP2; those who were negative for HLA-A2/A3 were randomly assigned to receive GM-CSF with or without AE37.

Dr. Mittendorf presented the primary analyses of the study’s GP2 and AE37 arms in 2014 at the American Society of Clinical Oncology’s Breast Cancer Symposium and its Annual Meeting, respectively. “Both vaccines were safe and stimulated an immune response,” Dr. Mittendorf said. “AE37 had its strongest efficacy in patients with triple-negative breast cancer, and we’re developing a trial of the vaccine for these patients. GP2 had its strongest signal in HER2-positive patients who had received trastuzumab.”

**E39 and J65**

The E39 vaccine is derived from folate binding protein, which is expressed on the surface of most breast and ovarian cancer cells. Studies performed at MD Anderson demonstrated that E39 produced a robust immune response in ovarian cancer patients; however, whether this response would exhaust the immune system and prove counterproductive was not known. To determine the optimal strategy for using the vaccine, Dr. Mittendorf and her colleagues have begun a clinical trial at MD Anderson in which patients with breast or ovarian cancer receive E39 and J65, an attenuated version of E39, on various dosing schedules. Patients are randomly assigned to receive monthly injections according to one of three regimens: six injections of E39, three injections of E39 followed by three of J65, or three injections of J65 followed by three of E39.

“This trial will determine whether it’s better to come in hard with E39 for a few doses and then give J65 to soften the blow or start soft with J65 and ramp up slowly to E39,” Dr. Mittendorf said.

**Immune checkpoint inhibitors**

The relatively new class of drugs that inhibit immune checkpoints—cytotoxic T lymphocyte antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1), and the PD-1 ligand (PD-L1)—has extended survival for patients with metastatic melanoma and has been found to be effective against several other types of cancer, including breast cancer.

Jennifer Litton, M.D., an associate
Triage Program for Triple-Negative Breast Cancer

Triplet-negative breast cancers—those that do not express estrogen receptors, progesterone receptors, or HER2—have about a 50% chance of responding to standard neoadjuvant chemotherapy. For patients whose cancer does not respond and who therefore are at higher risk for recurrence, researchers at MD Anderson Cancer Center have developed a triage program to find an appropriate experimental treatment.

At MD Anderson, patients with triple-negative breast cancer undergo genomic testing and then begin standard neoadjuvant chemotherapy. Dr. Litton said the triage program is similar in design to the I-SPY 2 TRIAL (see “Novel Trial Design Streamlines Development of Breast Cancer Therapies,” OncoLog, April 2015), except that patients begin treatment right away instead of waiting 2–3 weeks for the results of the genomic tests. When the results arrive, physicians also have clinical data that indicate whether the cancer is responding to standard chemotherapy.

“In the triage protocol, we can look at the early response and, for patients whose cancer is responding, we continue standard therapy and observe them; these patients will likely do well,” Dr. Litton said.

“But we know that patients whose cancer does not respond to those initial doses of first-line treatment have only a 5% chance of a complete pathologic response to standard second-line treatment, and these patients are assigned to a clinical trial based on the results of the genomic tests. We’re in the process of opening a series of phase II trials of new treatments—including immunotherapy—for triple-negative breast cancer.”

Dr. Litton said that MD Anderson is the only institution in the United States to offer such a program for patients with triple-negative breast cancer.

Other immunotherapy approaches

“Our immunotherapy studies have moved from just vaccines to include checkpoint inhibitors and other immunotherapy strategies,” Dr. Mittendorf

[Continued on page 8]
Hospital Patient Advocates Provide Support

Advocates serve as liaisons between hospitals and patients

Hospital visits often are stressful and confusing for patients and their loved ones. Fortunately, help is available from patient advocates. These hospital employees specialize in making the hospital journey go as smoothly as possible for patients and their families.

What patient advocates do
Patient advocates are a primary liaison between patients and the hospital. The advocates are there to help patients and their families or caregivers resolve problems they encounter at the hospital.

Patient advocates’ job descriptions vary from hospital to hospital, as do their titles. They may be known as patient representatives, patient liaisons, consumer advocates, crisis resolution specialists, or ombudsmen.

Whatever the job title, the patient advocate is responsible for addressing patients’ concerns, complaints, or grievances. In fact, all hospitals accredited by the Joint Commission are required to have a complaint resolution process that includes advocates.

At The University of Texas MD Anderson Cancer Center, for example, every person who is hospitalized or receives care as an outpatient is assigned a patient advocate.

“We meet with new patients during their first appointment,” said Jaymesson Bezerra, a patient advocate at MD Anderson. “We want to make sure they know their rights and responsibilities and have clear expectations.”

Patient advocates provide a much needed service. According to Mr. Bezerra, last year patient advocates at MD Anderson met face-to-face with approximately 16,500 new patients and handled 19,000 requests for assistance and 5,000 complaints.

How patient advocates help
In addition to giving patients an opportunity to express their complaints or concerns in a confidential setting, the patient advocates provide information about available resources, services, and patient rights and responsibilities.

Patients can contact their patient advocate directly to discuss a concern. These concerns vary widely. Many patients seek help with communication, scheduling, or wait times. Some patients need to have a hospital bill explained. Others are worried about the course of their treatments or the medications they’re receiving.

Patient advocates listen and offer appropriate help. They can explain hospital policies and procedures, assist in finding community services, provide information on insurance coverage, and discuss concerns the patient has about follow-up care at home.

A typical day for a patient advocate might include meeting new patients in the clinic, investigating and documenting inpatient or outpatient complaints, and meeting with the appropriate hospital staff members to try to resolve the issues.

Patient complaints might involve anything from a conflict with a hospital staff member to dissatisfaction with medical care. The patient advocate first listens carefully to the patient’s or family member’s concerns. Sometimes the advocate has the information needed to deal with the situation immediately. If not, the advocate will investigate further and ultimately try to solve the problem.

This could mean talking with other staff members or contacting an attending physician to resolve the patient’s issue. Collaboration—knowing whom to contact to help solve the patient’s problem—is a major part of the advocate’s job.

“We want to make sure the line of communication is clear between a patient and the medical team,” Mr. Bezerra said.

Following up on all complaints after their resolution is also part of the patient advocate’s job. If the patient feels that issues still need to be investigated and dealt with, the advocate will take further action.

The patient advocate also analyzes the complaints to determine if there is a pattern indicating a need for a change in hospital policy or procedures. If there is, the advocate works with other departments and the hospital administration to implement the changes.

Above all, the patient advocate treats the patient with dignity, respect, and consideration and acts on the patient’s behalf. Mr. Bezerra said, “We can be a voice for the patient.”

–K. Stuyck

FOR MORE INFORMATION
• Talk to your physician
• Visit www.mdanderson.org
• MD Anderson patients can call the Department of Patient Advocacy and Guest Relations at 713-792-7776

OncoLog, July 2015 ©2015 The University of Texas MD Anderson Cancer Center
said. “And as an institution, we have the opportunity to do more.”

For example, Dr. Ibrahim is the principal investigator at MD Anderson for an ongoing multi-institutional trial of the oral immunostimulant indoximod with taxane-based chemotherapy for patients with HER2-negative metastatic breast cancer. Indoximod inhibits the indoleamine 2,3-dioxygenase pathway, which suppresses T cell activity.

Also under investigation are agents that block the action of interleukin-8 (CXCL8), which has an immunomodulatory effect and is associated with breast cancer growth and metastasis. A trial of one such agent, reparixin, which binds to the CXCL8 receptor CXCR1, is under way at MD Anderson and other institutions.

Preclinical studies of promising therapies also are under way. For example, Dr. Mittendorf said, Laurence Cooper, M.D., Ph.D., a professor in the Division of Pediatrics, is investigating the use of T cells modified with chimeric antigen receptors (see “Sleeping Beauty’ Technique Modifies T Cells to Treat B Cell Malignancies,” OncoLog, May 2014) against triple-negative breast cancer.

Also on the horizon are studies of antiphosphatidylserine antibodies, which have been shown to improve the activity of taxanes against breast cancer. Likewise, studies are being planned of agents that stimulate the activity of natural killer cells and therefore may enhance the response to standard breast cancer drugs such as trastuzumab and toll-like receptor agonists.

Looking ahead

As researchers continue to elucidate the role of immunotherapy against breast cancer, clinical trials are increasingly becoming available for patients with metastatic disease and those with difficult-to-treat subtypes at high risk of recurrence.

“There are trials that are open or in the process of opening for patients with triple-negative breast cancer,” Dr. Tripathy said. “The field is moving rapidly, and we hope that immunotherapy can prevent recurrences.”

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