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David Galloway

Ann Sutton

Katie Prout Matias

Donna R. Copeland PhD

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OncoLog

REPORT TO PHYSICIANS

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Pediatric Oncologists Search for More Effective Drugs to Treat an 'Orphan Disease'

by David Galloway

Ewing's sarcoma is what is known as an orphan disease. Drug companies don't get very excited about finding cures or treatments for diseases that affect only 200 to 300 new patients each year.

"It takes millions of dollars to develop a new drug. If it's only going

to be useful in 200 patients a year, it's not going to really get the payback, and the stockholders won't be happy," said Eugenie S. Kleinerman, M.D., head of the Division of Pediatrics at The University of Texas M. D. Anderson Cancer Center. The National Institutes of Health consider an estimated 6,000 diseases affecting about 20 million people in the United States to be orphan diseases, meaning that each disease affects fewer than 200,000 Americans or that there is no reasonable expectation that the costs of developing drugs for their treatment

could be recovered from the sale of the drugs.

Meeting both of the above criteria, the Ewing's sarcoma family of tumors is rare indeed. Many oncologists will work their whole lives without ever seeing these tumors that invade the bones or soft tissues. The small, undifferentiated, round cells with a common chromosomal abnormality are most frequently seen in the long bones of the arm or leg, in the flat bones of the ribs or pelvis, or in the spine; however, they can develop in any bone, and 10% to 15% of these

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Researchers in the Division of Pediatrics are studying the biology of Ewing's sarcoma, a very rare pediatric cancer, in an effort to find effective treatments among drugs developed for other diseases. One such drug is trastuzumab, an antibody directed against HER2. Here (from the left),

Dr. Zhichao Zhou, a research investigator in the Division of Pediatrics, **Dr. Eugenie S. Kleinerman**, head of the division, and graduate research assistant **Geoffrey Kannan** look at a Northern blot of HER2 expression in Ewing's sarcoma cell lines.



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Oncologists Search for Effective Treatments for Ewing's Sarcoma

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tumors arise outside of bone. Most patients are 10 to 20 years old and white or Hispanic (the disease is very uncommon among African Americans). Patients may present with pain, stiffness, or tenderness, along with swelling or a mass in the area of the tumor; weight loss and fever are also common. Ewing's sarcoma is frequently diagnosed after a pathologic fracture of a bone weakened by a tumor. The two-year metastasis-free survival rate for patients with Ewing's sarcoma is only about 40% (the five-year survival rate for patients who do not have metastatic disease at presentation is 60%), and the disease tends to metastasize to the lungs, bones, and bone marrow, often resulting in death very quickly.

The current standard treatment for Ewing's sarcoma consists of induction chemotherapy (vincristine, doxorubicin, and cyclophosphamide), followed by surgical resection of the tumor, radiotherapy, or both. Further chemotherapy is given after local therapy. This combination has not significantly improved disease-free survival rates, however, so researchers are looking for other treatments.

Dr. Kleinerman hopes a drug used to treat breast cancer also will be effective against Ewing's sarcoma. "In the lab, we've shown that one of the proteins that is overexpressed in breast cancer, HER2, also is overexpressed in Ewing's sarcoma. And we've shown that if you down-regulate HER2, the Ewing's cells become more sensitive to chemotherapy." That would mean patients could be treated with lower doses of chemotherapy—and, in turn, experience fewer toxic effects—while still receiving the full benefit from the chemotherapy treatment. Dr. Kleinerman plans to test this hypothesis using trastuzumab (Herceptin), a recombinant humanized mouse monoclonal antibody directed against HER2, in a mouse model of Ewing's sarcoma. If trastuzumab proves effective in vivo, clinical trials could be planned.

"The advantage is that this is a drug that's already commercially available," Dr. Kleinerman said. "Nobody has to develop it. It's in the clinic for breast cancer, so the fact that we have a rare disease doesn't matter. And that's really

"There needs to be funding for sarcoma research just like breast cancer research, particularly because we've made no major advances in 20 years in this disease."

—Eugenie S. Kleinerman, M.D.,
division head, Division of Pediatrics

where I've turned to. I think the best approach for these rare diseases is to try to understand the biology and see if there are any other tumors where agents have been developed that we can use rather than developing our own."

Dr. Kleinerman also is enrolling newly diagnosed Ewing's sarcoma patients in a phase II trial of a liposome-encapsulated lipophilic disaccharide tripeptide derivative of muramyl dipeptide (ImmTher) that stimulates white blood cells to kill tumor cells. "We had some success with a sister compound called MTP [muramyl tripeptide phosphatidylethanolamine] in osteosarcoma, and because Ewing's sarcoma spreads to the lungs like osteosarcoma, we thought maybe this new drug would have some value," Dr. Kleinerman said. Unfortunately, the company that made ImmTher has ceased its production; however, all the remaining stockpile of the drug was shipped to M. D. Anderson. "So, we have the world's supply of ImmTher," Dr. Kleinerman said. "There is no more."

Cynthia E. Herzog, M.D., an associate professor of pediatrics at M. D. Anderson, explained that ImmTher stimulates macrophages. "The principle behind this is that if you treat patients until they have only microscopic disease, you could then give them an agent that stimulates the immune system and hopefully have the immune system take care of the microscopic disease. For Ewing's, one of the prime sites of metastasis is the lungs, which is an area that is rich in macrophages that are stimulated by this agent, and so our hope is that it will have some

activity and help prevent recurrences. We're still accumulating patients, so it will be a little while before we have an answer to this question."

The poor prognosis for patients who have had a recurrence of Ewing's sarcoma is of particular concern to researchers. Dr. Herzog is opening another phase II trial for such patients to test a topoisomerase I inhibitor known as exatecan mesylate (DX-8951f). "It's a third-generation drug, and the two previous generations—topotecan and irinotecan—have both shown some activity. This one [DX-8951f] seems to have activity even in tumors that are resistant to its predecessors," Dr. Herzog said.

Unfortunately, Dr. Kleinerman said, very little current research is focusing on Ewing's sarcoma. A fact of life in the world of research is that laboratories need funding. Dr. Kleinerman said there are "large pots of money" available for the study of breast cancer, prostate cancer, lung cancer, and colon cancer, so researchers often switch their focus to areas where they can get the funding. "We've seen a great switch to breast cancer research over the past 10 years, which is good, because there have been a lot of breakthroughs," Dr. Kleinerman said. "But at the same time, nobody's interested in Ewing's sarcoma, because there are no special funding opportunities."

Dr. Kleinerman believes research into orphan diseases calls for special incentives. "I think that somebody has to make the argument that there needs to be funding for sarcoma research just like breast cancer research, particularly because we've made no major advances in 20 years in this disease," she said. "I think it's important that perhaps the federal government get involved in making it more attractive for drug companies to develop new therapies for these rare diseases by offering patent benefits or expedited approval. But it's very clear to me that if you just leave it to the free market, we're not going to see any improvement." ●

FOR MORE INFORMATION, contact Dr. Kleinerman at (713) 792-8110 or Dr. Herzog at (713) 745-0157.

Collaborative Studies Lead to Better Survival Rates in Young Patients with Rhabdomyosarcoma

by Ann Sutton

R Beverly Raney, Jr., M.D., has treated thousands of patients in the almost 30 years that he has been practicing medicine. Some of his patients he remembers better than others; one he will never forget.

Several years ago, Dr. Raney treated a young boy with rhabdomyosarcoma who had a tumor in his thigh. At that time—a time when more than half of patients with rhabdomyosarcoma died of the disease—the standard treatment for tumors of the extremities was amputation. The boy's leg was removed, but the treatment team later found lymph node involvement higher up, in the pelvis.

"What is the point of taking off a leg if you've already got disease above it?" asked Dr. Raney, a professor in the Division of Pediatrics at The University of Texas M. D. Anderson Cancer Center. "A year later, he had lung disease and died. But he could have

lived that year with both of his legs rather than as an unhappy four-year-old amputee."

That experience led Dr. Raney to study ways to improve the outcomes of patients with rhabdomyosarcoma. He became a member of the Intergroup Rhabdomyosarcoma Study, now called the Soft Tissue Sarcoma Committee (STSC), a collaboration between members of the Children's Cancer Group and the Pediatric Oncology Group (now called the Children's Oncology Group) that investigates rhabdomyosarcoma and undifferentiated sarcoma in patients less than 21 years old. Primarily because of the research conducted by the STSC, survival outcomes have substantially improved for children with this rare disease—the overall five-year survival rate has risen from about 55% in the mid-1970s to 70% today, and patients with localized disease now have an 85% survival rate.

The STSC has completed several studies—studies I through IV, plus additional pilot through IV studies for patients with advanced disease. Each study is a separate protocol that builds on the findings of the previous studies.

Study V began recruiting patients in 1997 and, according to Dr. Raney, should be completed within the next three years. Study VI is already being planned. Recent emphasis, such as in study V, has been on shrinking the tumor with chemotherapy or radiation therapy before surgery so that it can be removed with the least damage to organ function or patient appearance.

"We try to do major surgery at the beginning, provided it is safe and won't impair function significantly. But if it is not considered safe or would lead to a functional or cosmetic result that's not appropriate, we try to shrink the tumor first, nonsurgically, and then consider removing the residual tumor, if that's feasible, later," said Dr. Raney.

In studies I-III, patients were grouped by the extent of both their disease and the initial surgical resection. However, over the years, the STSC developed a new staging system for rhabdomyosarcoma that was not dependent on the surgeon's decisions about resection or on pathologic assessments of the tumor. The new system is based on the tumor-node-metastasis (TNM) system developed by the American Joint Committee on Cancer and categorizes patients by site of the primary tumor, tumor size, and lymph node involvement or metastasis.

Based on the results of STSC studies, the current standard of care for most patients with rhabdomyosarcoma is a combination of chemotherapy (vincristine, dactinomycin, and cyclophosphamide), surgical excision, and radiation therapy.

"The big issues for children with this disease are to try to figure out how to preserve life and also preserve function. A lot of these tumors arise above the clavicle, in the head and neck—visible parts of the body. You cannot do major surgery on a child's face just because it's a good idea to take all the tumor out. It is a bad idea to leave them with a face that is very deformed," said Dr. Raney.

One of the techniques used most recently in patients with rhabdomyosarcoma is sentinel lymph node mapping. "In past years, people thought that rhabdomyosarcoma rarely spread to lymph nodes. That was really because no one was

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— R. Beverly Raney, Jr., M.D.,
professor, Division of Pediatrics

Studies Lead to Better Survival Rates in Patients with Rhabdomyosarcoma

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doing a biopsy on them. After doing sentinel lymph node mapping for melanoma, I thought that we could use the same technique for rhabdomyosarcoma of the extremities and chest wall. So we started using the lymphoscintigraphy and blue dye just as in melanoma and found out that it works well. Instead of only 12% of rhabdomyosarcoma patients having positive nodes, it turns out that 50% have positive nodes and thus require radiation therapy to the regional nodes," said Richard Andrassy, M.D., a pediatric surgeon, chair of the Department of Surgery at The University of Texas Health Science Center at Houston Medical School, and member of the STSC.

Second-look surgery, in which a surgeon examines the disease site after chemotherapy to see if any cancer remains, has been another successful technique in patients with rhabdomyosarcoma. Sometimes less invasive methods, such as computed tomography, cannot detect all remaining cancer. "Second-look surgery is particularly helpful in areas that are hard to see, such as the retroperitoneum and abdomen," said Dr. Andrassy.

Rhabdomyosarcoma is cancer of striated muscle that arises from embryonic mesenchyme. Cells resemble rhabdomyoblasts (fetal premuscle cells). Approximately 350 patients 0 to 20 years old are diagnosed with the disease each year in the United States, and

"We have come a long way toward understanding the disease and improving the outcome of multidisciplinary care for patients with rhabdomyosarcoma."

**– R. Beverly Raney, Jr., M.D.,
professor, Division of Pediatrics**

Dr. Raney estimates that about 80% of those patients enter an STSC trial. Overall, two thirds of children with rhabdomyosarcoma will survive with proper treatment.

Embryonal rhabdomyosarcoma is the most common type (60% to 70% of cases), occurring mostly in the head and neck and genitourinary tract, usually in infants and young children. Botryoid rhabdomyosarcoma is a subtype of embryonal rhabdomyosarcoma that usually occurs in infants and is most commonly found in the vagina and bladder. Spindle cell rhabdomyosarcoma, another embryonal disease, accounts for approximately 10% of all rhabdomyosarcoma cases. It is usually found in the paratesticular area. Approximately 20% of rhabdomyosarcoma cases are of the alveolar type, which occurs mostly in the large muscles of the trunk, arms, and legs and is most common in older children and adolescents. Alveolar rhabdomyosarcoma is the most aggressive and dangerous type. The remaining subtype of rhabdomyosarcoma is pleomorphic, which occurs mainly in adults 30 to 50 years old.

"It's a very complex disorder that can occur anywhere in the body. The only place it doesn't originate is within a bone. But it can spread to bones, so we have to think about bones when looking at this disease overall," said Dr. Raney.

Environmental risk factors for rhabdomyosarcoma may include parental use of marijuana or cocaine, intrauterine x-ray exposure, and exposure to alkylating agents. Genetic factors include a family history of Li-Fraumeni syndrome or a personal history of Beckwith-Wiedemann syndrome or neurofibromatosis. Rhabdomyosarcoma has also been associated with p53 mutations, chromosome 13 translocation, Rubinstein-Taybi syndrome, and Gorlin's syndrome.

Primary tumors located in the nonparameningeal head and neck, paratestis, vagina, orbit, and biliary tract have the most favorable outcome. In fact, the cure rate for orbital rhabdomyosarcoma is almost 100%.

"Those patients have a very good outlook, probably because you can see

a 3- or 4-mm tumor if it is sticking out from under an eyelid," said Dr. Raney. The standard treatment for orbital rhabdomyosarcoma in the United States is chemotherapy and radiation therapy. Physicians in Europe, however, are wary of administering radiation therapy to the eye because it can cause cataracts.

The STSC is currently evaluating two new agents, topotecan and irinotecan, for the treatment of rhabdomyosarcoma, particularly the alveolar subtype. "This is an ongoing major area of interest because the survival rate for most of these patients is 50% to 60%," said Dr. Raney.

For patients whose tumors have failed to respond or have recurred after initial therapy, researchers are studying combinations of active drugs that have not been previously administered. Two of these new agents, which are being evaluated for the treatment of patients with recurrent rhabdomyosarcoma, are available at only a few institutions in the United States, including M. D. Anderson. One of them is lipovincristine, a liposomal formulation of vincristine that is released more slowly in the body and can be given less frequently. Patients who have been treated with regular vincristine can still have tumor shrinkage after therapy with lipovincristine. The other drug is called exatecan, which is a member of a relatively new class of topoisomerase I inhibitors that includes topotecan. Each of these new drugs can be given in the outpatient setting, which is usually more convenient and less expensive than inpatient treatment.

"We have come a long way toward understanding the disease and improving the outcome of multidisciplinary care for patients with rhabdomyosarcoma," said Dr. Raney. "The search for new methods of cure and new active drugs, together with improvements in surgery, radiation therapy, and supportive care, continues here in the Division of Pediatrics and beyond." ●

**FOR MORE INFORMATION, contact
Dr. Raney at (713) 792-6624.**

Protecting the Heart and Gastrointestinal Tract from Treatment-Associated Damage Is an Important Element of Cancer Care

by Katie Prout Matias

Patients who successfully undergo treatment for cancer could find themselves battling a new illness later on. Because of the inherent toxicity of chemotherapy and problems associated with radiation therapy, the possibility of organ damage in patients with cancer is a very real concern.

Owing to their locations and functions, the heart and the gastrointestinal (GI) tract can be adversely affected by treatments for many kinds of cancer. For example, damage to the heart is most commonly associated with chemotherapy for breast cancer and radiation therapy for lung cancers. The GI tract can be affected by treatments for head and neck, cervical, and prostate tumors, as well as by primary cancers of the esophagus, colon, stomach, and pancreas, among others.

Treatment-related cardiac damage

Chemotherapy and radiation therapy can damage the heart directly. Myocardial depression is associated with some forms of chemotherapy, whereas other agents can cause ischemia, hypotension, and rhythm disturbances. Radiation is associated with pericarditis and, rarely, ischemic heart disease. Much of the cardiac damage seen following cancer treatment is mild, but it is nevertheless present and can exacerbate subsequent damage associated with infections, excessive alcohol ingestion, or pregnancy.

“That is the concept of sequential stress, which was first described here at M. D. Anderson. The first stress is the chemotherapy-associated damage, and the second stress is the additional

damage associated with a variety of insults. All of the damage is additive and results in cardiomyopathy. Because of the subclinical damage caused by chemotherapy, you get an exaggerated reaction later on that can be very, very troublesome and in some instances can cause heart failure and even death,” said Michael S. Ewer, M.D., M.P.H., J.D., a professor in the Department of Cardiology at The University of Texas M. D. Anderson Cancer Center.

Anthracycline antibiotics, such as doxorubicin and daunorubicin, present the most notorious threat to the heart. The exact mechanism behind the cardiotoxicity of anthracyclines is still being researched, but modalities have been developed that lessen treatment-associated damage. “Since cardiac damage probably starts from the very first dose, it is prudent to think about protection at the beginning and not after you begin to recognize that some damage might have occurred,” said Dr. Ewer.

Preventing and treating cardiotoxic effects

One way to prevent or reduce the toxic effects of a drug is to limit the total dose given; however, giving a lower dose may make the drug less effective in some patients. Researchers at M. D. Anderson developed a technique whereby some forms of cardiotoxic chemotherapy are administered as a continuous infusion over 48 to 96 hours. This method reduces cardiotoxicity without significantly lowering the drug’s efficacy.

In one of several studies comparing bolus regimens with continuous infusion, 82 patients with soft tissue carcinomas were randomly assigned to receive



Protecting the heart from damage due to chemotherapy should be a priority from the very beginning of treatment, according to Dr. Michael S. Ewer, a professor in the Department of Cardiology.

doxorubicin as a bolus or as a 72-hour continuous infusion. Cardiotoxic effects were seen in 61% of the patients receiving the bolus regimen at a median cumulative dose of 420 mg/m², compared with only 42% of those receiving the continuous infusion at a higher median cumulative dose of 540 mg/m².

“It seems to be that the peak plasma level is more likely to cause cardiac damage, whereas the total amount given leads to tumor control,” said Dr. Ewer. “So if you give the same amount over a longer period of time, you have a lower peak in the plasma level, and that seems to be associated with less cardiac damage.”

Oncologists are also finding promise in the administration of protective

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Preventing and Controlling Damage to the Heart and GI Tract

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agents such as iron chelators and in the use of anthracycline analogues or anthracyclines that are less cardiotoxic than is doxorubicin. The latest research, however, focuses on the use of liposomal formulations of standard drugs. “The liposomal preparations encapsulate the active drug and release it at the tumor location,” said Dr. Ewer. Studies have shown that liposomal formulations cause fewer cardiotoxic effects than do unencapsulated drugs and demonstrate excellent antitumor efficacy.

Other encouraging news comes from a study recently conducted at M. D. Anderson, which found that standard therapies for heart failure such as ACE-inhibitors, beta-blockers, diuretics, and inotropic agents control some of the manifestations of chemotherapy-induced heart failure.

Effects of radiation therapy on the GI tract

Like the heart, the gastrointestinal tract is susceptible to long-term, treatment-associated damage, especially from radiation therapy. In the narrow tubal structures of the GI system, stricturing is perhaps the most common problem. Stricturing occurs as the inflamed organ begins to heal; the scar contracts, narrowing the passageway.

In patients receiving radiation therapy for chest and head and neck cancers, the esophagus is particularly susceptible to stricturing. “The esophagus can get in the way as an innocent bystander,” said Patrick Lynch, M.D., J.D., associate professor in the Department of Gastrointestinal Medicine and Nutrition at M. D. Anderson.

Similarly, radiation therapy for prostate and cervical cancers can cause damage to the lower colon and rectum. “Unlike the esophagus, which mainly has stricturing as a problem, in the rectum, the problem is usually bleeding,” said Dr. Lynch. “Patients develop vascular ectasias, dilated blood vessels in the rectum that are very fragile and bleed very easily.”



“Although most of our efforts are oriented toward improving outcomes—reducing cancer death and local recurrence—a lot of our focus is quality of life.”

**– Patrick Lynch, M.D., J.D.,
associate professor, Department of
Gastrointestinal Medicine and Nutrition**

Treating strictures and preventing radiation damage

Dr. Lynch said that in cases of stricturing, an endoscope is used to dilate the constricted tube; argon plasma coagulation and cauterization are effective in treating bleeding. In more simple cases of inflammation, topical steroids and acid-blocking medications work.

Like treatment-related cardiomyopathies that develop years down the road,

GI problems can occur or recur long after the treatments are over. “Strictures can be chronic problems that keep bringing folks back over and over,” said Dr. Lynch. “Dilation is something that has to be done over and over as an alternative to surgery.”

Whereas researchers have already developed several promising techniques to prevent chemotherapy-related heart damage, preventing radiation damage to the GI system has proven more difficult. One technique involves using a “belly board” to move parts of the abdomen away from the field of radiation. The board has a hole cut out of it that allows the abdomen to fall through it when the patient lies prone. “One of the biggest problems is stricturing and damage to the small bowel,” said Dr. Lynch. “The board uses gravity measures to get the small intestine out of the way of the radiation.”

Another way to protect the GI system is to give chemoradiation treatments before surgery instead of after, because once the operation is performed, the organ is already susceptible to scarring and is more likely to stricture when given chemoradiation. According to Dr. Lynch, most of the physicians and researchers at M. D. Anderson believe that giving radiation treatment before surgery improves the outcome and reduces many of the toxic effects.

“Although most of our efforts are oriented toward improving outcomes—reducing cancer death and local recurrence—a lot of our focus is quality of life, reducing GI toxicities and complications,” said Dr. Lynch.

While cancer treatments continue to be inherently toxic, finding ways to prevent or heal damage, and thus improve the quality of life for survivors of cancer, remains an important aspect of cancer care. ●

FOR MORE INFORMATION, contact Dr. Ewer at (713) 745-2216 or Dr. Lynch at (713) 794-5073.



Conquering the Pain of Cancer

Pain is one way the body has of telling us something is happening inside us.

Cancer pain can be caused by the growth of a tumor and by the side effects of treatments such as chemotherapy.

However, unrelieved pain does not have to be accepted as a normal part of having cancer, according to the American Cancer Society. Pain may worsen feelings of weakness, and it may interfere with your enjoyment of life and your ability to sleep and eat. It may even interfere with healing.

What should I do if I have pain?

Describe your pain to your health-care provider. There is no other way for your health-care provider to know how much or what kind of pain you have. Tell your doctors and nurses where you feel pain, and point to the place on your body or on a picture of the body. Describe what kind of sensation it is (sharp or dull, steady or pulsating, shooting or in one spot, burning, fullness, numbness, tingling, tightness, etc.); if it varies with the time of day, with a particular movement, or with general activity; and any possible “triggers” that start the pain.

Talk to your doctor about your concerns about pain medicines.

Many patients are uncomfortable asking for pain medication or for a higher dose because they fear becoming a drug addict. If you take opioid pain medication, your body will most likely become used to the medication (develop a tolerance), and you will need a higher dose to feel the same relief that a lower dose used to give you. Tolerance to pain medication and physical dependence are different from psychological dependence or drug abuse. Some patients are concerned about the side effects that opioids can cause, such as nausea, constipation, and difficulty thinking clearly. If side effects occur, a

change in the dosage or in the particular medication can help. Your doctor often will prescribe medications just for the side effects.

What is breakthrough pain?

Many people experience pain once in a while even after they have begun taking pain medicine regularly. This intermittent pain is called “breakthrough” pain because it “breaks through” the effects of the regular pain medication. If you experience this kind of pain, it does not mean that the regular pain medicine is not working. Breakthrough pain does not usually last very long but can be very intense. Certain fast-acting pain medications and techniques such as guided imagery and distraction can be very helpful in treating this kind of pain.

Keep your doctor updated about changes in your pain and in the medication’s ability to control it.

Because pain is one of the body’s ways of telling us what is happening, pain can help your doctor understand how your cancer is responding to treatment and how your whole body is responding to the cancer and to treatment. Also, the sooner your pain is treated, the better your chances of getting relief. If you wait, the pain medication will have to “catch up” with your pain, possibly requiring more than one dose of pain medication before you feel relief. You may have to wait a couple of hours before the second dose, and that is a long time to be in pain! Different medications may be tried until your doctor finds the one or ones that work best for you at a particular time.

Many ways to treat pain are available.

In addition to the different kinds of pain medications, some patients have found relief by using complementary techniques to ease pain. These techniques can be used at the same time as

pain medication. Some patients have found comfort through acupuncture and massage, which are available in many communities. Self-hypnosis, guided imagery, and biofeedback are pain management techniques that patients can learn from trained therapists through individual or group instruction. M. D. Anderson Cancer Center’s Place...of Wellness offers classes in these and other techniques. You do not have to be a patient at M. D. Anderson to take these classes. If you are not able to come to M. D. Anderson, look in your community for spas and health clubs that offer instruction in similar mind-body techniques.



Ask to see a pain management specialist.

Just as some doctors specialize in the treatment of cancer or in the treatment of a certain kind of cancer, other doctors specialize in the treatment of pain. You can see a pain specialist on your own or ask your doctor to consult with a pain specialist if you feel you would like more options to help treat your pain than the ones your doctor offers you. These options may include other medications or certain anesthetic injections or surgical procedures for pain.

Above all, don’t suffer in silence. Tell a doctor or nurse about any pain that you are having, and let them know when your pain medications aren’t working. Remember, treatments for pain only work when they are used. ●

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

 **(800) 392-1611** within the United States, or

 **(713) 792-6161** in Houston and outside the United States.

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DiaLog

Recognizing and Treating Cognitive Dysfunctions in Survivors of Childhood Cancers

Donna R. Copeland, Ph.D.
Professor, Department of Pediatrics

Even though most children with cancer will survive, they are at increased risk for long-term cognitive sequelae as a consequence of central nervous system (CNS) involvement and treatment. Brain functions most likely affected include attention/concentration, intelligence, memory, psychomotor abilities, and academic skills. Deficits can be progressive, and as cancer survivors enter adulthood, unemployment becomes common.



CNS cancers are treated with cranial radiation therapy (CRT) or chemotherapy. The prophylactic treatment of CNS metastases in patients with leukemia or lymphoma involves a much lower dose than that used to treat primary CNS tumors. Nevertheless, neuropsychological studies have confirmed that these lower doses of CRT can still result in significant cognitive impairment. The effects of chemotherapy administered to the CNS may be much less than those associated with CRT, but academic declines and attention deficits are still observed.

Evidence exists of an association between attentional abnormalities and structural abnormalities in the brain following CNS treatment. In studies of childhood leukemia survivors, neuropsychological tests and imaging scans demonstrated that 1) problems in reaction time, shifting

attention, and sustained attention were common; 2) children with more severe CNS lesions (i.e., intracerebral calcifications) had the greatest deficits in these tasks; and 3) problems with attention were significantly correlated with problems in higher-order cognitive processes such as memory and learning. More recently, similar findings from a much larger sample of leukemia survivors showed low scores on Freedom from Distractibility Factor (Wechsler scales), arithmetic computation, and mental concentration tests—all of which correlated with abnormalities found in imaging studies.

So the evidence is clear that survivors of childhood leukemia and intracranial tumors are at risk for learning difficulties. We can help these patients, however. Physicians who follow up on survivors of childhood cancers can make a point of asking them how they are faring in school or work. If difficulties are reported, I recommend a referral to a neuropsychologist who is familiar with the effects of childhood cancer and its treatment. The neuropsychologist can evaluate the patient to ascertain the cognitive functions involved and take appropriate action, which is likely to entail a consultation with the young person's school. Ideally, a cognitive remediation program will be available. These programs are designed to teach the cancer survivor ways to compensate for deficits. Also, stimulants are sometimes effective in ameliorating the attentional deficits that occur as a result of CNS disease and treatment, and tutoring, special education classes, or both can help students with school subjects.

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