New Approaches to Managing Tumors of the Pituitary Gland Offer Patients Hope

by Ellen McDonald

Patients with tumors of the pituitary gland generally find themselves in a uniquely frustrating position: On the one hand, they learn the good news that many of these tumors are asymptomatic and that death from such tumors is very rare. On the other hand, they soon learn that they face a lifetime of (Continued on next page)
potentially debilitating illness often necessitating multiple interventions, lifelong hormone-replacement therapy, and long-term follow-up care.

At The University of Texas M. D. Anderson Cancer Center, several advances in treating pituitary tumors offer new hope to patients: Successful surgical resections of these tumors are becoming more common, a clinical trial comparing two drugs used in the medical treatment of acromegaly is under way, and the projected opening of the institution’s proton therapy facility in 2006 may provide an improved means of irradiating pituitary tumors without damaging normal surrounding tissues.

Understanding the pituitary tumor

Tumors of the pituitary gland are generally slow-growing benign adenomas that are classified as either functional (60%), meaning that they hypersecrete one or more hormones, or nonfunctional (40%), meaning that they secrete no hormones but instead are just masses of cells. These tumor masses can compress the pituitary gland itself, which can cause hormone deficiency, or adjacent structures such as the optic nerve, which can lead to disturbances in and loss of vision.

“Although pituitary tumors generally do not metastasize and do not have mitotic features, they can sometimes behave in a very locally aggressive manner,” said Rena V. Sellin, M.D., a professor in the Department of Endocrine Neoplasia and Hormonal Disorders at M. D. Anderson. “Although usually benign, they can recur again and again.”

According to Steven G. Waguespack, M.D., an assistant professor in the Department of Endocrine Neoplasia and Hormonal Disorders, there are three questions that should be asked when treating patients with these tumors: 1) Is the tumor making a hormone that is causing a clinical syndrome—growth hormone in acromegaly, adrenocorticotropin hormone in Cushing’s disease, or prolactin, which can cause hypogonadism (low estrogen or testosterone levels) and abnormal breast milk production?; 2) Is the tumor preventing the pituitary gland from working normally, thereby causing one or more hormone deficiencies?; and 3) Is the tumor mass causing visual loss or affecting other cranial nerves?

The etiology of pituitary tumors is generally unknown, and their incidence has been variously reported. “The incidence of pituitary tumors across the board is about one in seven people,” said Ian E. McCutcheon, M.D., a professor in the Department of Neurosurgery at M. D. Anderson and president of the Pituitary Network Association who recently helped conduct a meta-analysis of published studies on the incidence of these tumors, which appeared in Cancer. However, only 5% of people with pituitary tumors will ever have any symptoms related to the tumor.

Treatment approaches

Treatment of benign pituitary tumors consists of surgery, radiotherapy, medical therapy, or a combination of these methods. The indications for surgery depend on the size and type (functional or nonfunctional) of the pituitary tumor involved. “Usually, with the functional ones, we start with an operation to try to remove as much of the tumor as we possibly can because the disruption of excess hormone is typically causing profoundly negative changes for the patient,” observed Dr. McCutcheon. An exception to surgical treatment of functional tumors occurs in prolactinomas, which are generally responsive to medical therapy. “In the nonfunctional category,” Dr. McCutcheon continued, “the reason to operate is to protect the optic system from a large or expanding tumor.”

According to Dr. McCutcheon, approximately 95% of the operations performed on pituitary tumors at M. D. Anderson use a transsphenoidal approach, following a route along the inside of the nose; the remaining 5% are craniotomies. Dr. McCutcheon pointed out that the first transsphenoidal surgery in Texas was performed at M. D. Anderson by Milam E. Leavens, M.D., former Ashbel Smith professor emeritus of neurosurgery in the Department of Neurosurgery (and Dr. McCutcheon’s predecessor).

Pathology

Lauren A. Langford, M.D., an associate professor in the Department of Pathology at M. D. Anderson, noted that 10% to 15% of primary brain tumors diagnosed each year are pituitary tumors. Pathologists determine which hormones are being produced by the tumor cells and what is in the cells “to complement the data obtained by the endocrinologist’s full battery of hormonal tests,” she explained. In addition, results from immunohistochemical stains can be obtained quickly; a special reticulum stain performed during surgery to see whether the subunits of the pituitary gland are intact takes about 15 minutes. “If they are intact, then we think the specimen is probably normal tissue,” she said. This information can be invaluable to the operating surgeon, not to mention the patient. Pathologists also use the fact that pituitary adenomas shed their cells to distinguish them from normal tissue. Dr. Langford shares the following advice with her trainees: “Pituitary tumors are very difficult; spend a lot of time on them, look at a lot of them, because you have a person’s whole hormonal axis in your hand.”
Treating acromegaly

Patients with acromegaly have two to four times the death rate of those without the disease and generally live 10 years fewer, said Dr. Waguespack. “So we try to be as aggressive as possible to treat their disease.” He noted that although surgery can be curative for easily resectable microadenomas (tumors < 1 cm), most patients with acromegaly actually have larger tumors. “For these adenomas, particularly when the tumor is causing visual compromise, surgery is usually undertaken not so much in hopes of a cure but to alleviate the symptoms caused by the tumor size itself,” he said. Subsequent medical management is almost always required.

According to Dr. Waguespack, three types of medicine are available to treat acromegaly: The oldest drugs are the dopamine agonistic agents, which are used to treat prolactinomas and are effective in fewer than 15% of cases of acromegaly. The second type of agent is a somatostatin analogue called octreotide, which inhibits the pituitary somatotroph from making growth hormone. “This drug, which has been the most tried and true, is effective in lowering growth hormone levels in 65% of patients with acromegaly who receive it,” said Dr. Waguespack. The third type of medicine is the drug pegvisomant, approved for use in 2003, which does not have any direct effect on the tumor but blocks growth hormone at its receptor level, telling it not to make insulin-like growth factor 1, which is the main mediator of growth hormone action. According to Dr. Waguespack, studies of this drug have shown it to be more than 90% effective.

In a randomized clinical study, Dr. Waguespack is directly comparing pegvisomant with octreotide for the treatment of patients with acromegaly who have never received any medical therapy for their disease. This phase IV trial is the first comparative study of the two drugs used most often in the treatment of the disease. Dr. Waguespack expressed some concern about the “theoretical risks” of pegvisomant, in particular the possibility that when growth hormone is blocked at the receptor level, the pituitary tumor may eventually grow larger. “This risk does not typically exist with octreotide, which can cause tumors to shrink,” he said.

Dr. Waguespack also spoke enthusiastically about the improved ways of delivering radiotherapy to pituitary tumors that are now available, including forms of stereotactic radiosurgery: Both gamma knife and linear accelerator technologies provide targeted therapy to the tumor site, thus minimizing the radiation exposure of adjacent tissue and potentially eliminating the late effects of conventional radiotherapy, such as secondary brain tumors, neurocognitive effects, and hypopituitarism. Radiosurgery is performed on patients with pituitary tumors at M. D. Anderson by Dr. McCutcheon and his colleagues in the Division of Radiation Oncology. A high degree of precision can be achieved by using magnetic resonance imaging overlay and other technologies now available, but Dr. Waguespack reserved his highest praise for proton beam therapy and its promise of effecting a cure without damaging surrounding tissues. However, he cautioned, this is an area that has not been well studied in acromegaly and requires further clinical investigation.

Recently, Dr. Waguespack has seen a number of patients in their 20s with acromegaly. He does not relish the thought of placing them on 50 or more years of expensive medication: “In the future, particularly with younger patients, we are going to have to rethink acromegaly treatment algorithms, incorporating newer medications and technologies to actually attempt to cure patients of their acromegaly.”

The continual improvement in surgical techniques, the advances in medical therapy, and the promise of new types of radiotherapy will doubtless provide those treating patients with pituitary gland tumors with many more options for managing and perhaps even curing the disease.

For more information, contact Dr. Sellin or Dr. Waguespack at (713) 792-2841, Dr. McCutcheon at (713) 792-2400, or Dr. Langford at (713) 792-7935.
Needleless Chemotherapy
Safety and Efficacy of Aerosolized Chemotherapy

by Ann Sutton

No one enjoys getting a shot, and intravenous therapy can be even more traumatic for children, who may not fully understand why they must be stuck, sometimes repeatedly, with a needle. The development of the first corticosteroid inhaler in 1972 was a welcome change for patients with asthma, mostly children, who had previously been treated with oral epinephrine and intravenous aminophylline. Patients with cancer in the lung may soon experience a similar change in treatment—needleless chemotherapy that is almost as easy as breathing.

Researchers in the Division of Pediatrics at The University of Texas M. D. Anderson Cancer Center are investigating the safety and efficacy of delivering chemotherapy drugs via aerosol inhalation in pediatric patients. “Clearly, once we’ve improved the technology, giving aerosol is going to be a lot easier on children than us constantly having to stick something in their arms,” said Eugenie S. Kleinerman, M.D., division head and professor of pediatrics. Eventually, she said, “aerosol therapy could even be given at home, just like we treat asthma.”

Benefits of aerosolized therapy

If aerosol delivery is determined to be as safe and effective as intravenous delivery, treating disease at home would be one of its main advantages. In addition to eliminating the pain of needles, home-based aerosol therapy would allow the patient to avoid frequent trips to the hospital or clinic. “That’s what patients would like to not have to do. It interferes with their lives,” said Cynthia E. Herzog, M.D., an associate professor in the Division of Pediatrics.

Another benefit would be that aerosol delivery allows more of the drug to be absorbed than oral or intravenous delivery does because of the lung’s large surface area (an adult lung has the same surface area as a tennis court). Drugs are sometimes absorbed faster when administered by inhalation than by subcutaneous injection.

The most obvious benefit will be in treating patients with any kind of cancer in the lungs. “I think anything that goes to the lung can be treated, whether it’s lung cancer, melanoma that goes to the lung, sarcoma, or Wilms’ tumor—anything that’s in the lung,” said Dr. Kleinerman.

Researchers have found that patients receiving aerosolized chemotherapy experience fewer side effects because more of the drug stays in the lungs at the tumor site and less is distributed systemically. “By giving the therapy by aerosol, we can get higher concentrations [of the drug] in the lung, where the tumor is, and we can get less of a spillover effect in the blood,” said Dr. Kleinerman.
Current research

Dr. Herzog is principal investigator on a phase I/II trial investigating the effectiveness of aerosolized rubitecan (9-nitrocamptothecin) in the treatment of patients 10 to 25 years of age with any kind of cancer that has spread to the lungs. Rubitecan is an oral semisynthetic topoisomerase I inhibitor that has been studied in the treatment of pancreatic cancer. The drug is not water soluble, so it must be encapsulated in liposomes to allow it to travel through the bloodstream. Liposomal formulations of various insoluble drugs have been found to have potent antitumor effects in nude mice when administered intravenously, with no serious side effects.

The rubitecan will be administered from a nebulizer through a face mask while sitting under a scavenging tent (shown here) that filters and removes any drug particles that escape the face mask.

The rubitecan will be administered from a nebulizer through a face mask while the patient sits under a scavenging tent to contain the drug. Scavenging tents are similar to oxygen tents; air is drawn up from the bottom and filtered to remove any drug particles that escape the nebulizer or face mask. Patients breathe in the chemotherapy from a nebulizer through a face mask while sitting under a scavenging tent (shown here) that filters and removes any drug particles that escape the face mask.

In a previous phase I study conducted at M. D. Anderson, 25 patients (ages 33 to 84 years) with primary lung cancer and other kinds of cancer that had spread to the lungs underwent aerosol therapy with rubitecan. Researchers determined that the drug could be administered safely at a dosage of 13.3 µg/kg/day, five days a week for eight of every 10 weeks. A few of the most common adverse effects were cough, nausea, and fatigue. The dose-limiting toxicities were chemical pharyngeal mucositis and fatigue. If toxic effects no worse than grade 2 were found, the patient was allowed to continue the treatment at home with a portable air compressor.

Future applications

Theoretically, any agent could be delivered via aerosol. Dr. Kleinerman is currently researching the delivery of gemcitabine via aerosol in her laboratory. Researchers at M. D. Anderson are also investigating aerosol delivery of paclitaxel and polyethyleneimine with the p53 gene, which is mutated or altered in many human cancers.

Some researchers believe that gene therapy will be able to significantly increase the long-term survival of patients with lung cancer—something that surgery, radiation therapy, and chemotherapy have not been able to do for years—but developing aerosolized gene therapy—like any gene therapy—is challenging, requiring extra caution to prevent spillover into the environment. “That’s not ready for prime time,” said Dr. Kleinerman. “I’d say probably the chemotherapy, the aerosolized gemcitabine, is closer to being tested in the clinic than any of the gene therapy investigations.”

Aerosolized therapy is not new, but its use in treating cancer is cutting edge. “We’re at the end of the diving board, and we’re jumping off,” said Dr. Kleinerman. “Whether there will be water in the pool is the question.”

“I think there’s water in the pool; it’s a question of how deep,” suggested Dr. Herzog.

For more information, contact Dr. Kleinerman at (713) 792-8110 or Dr. Herzog at (713) 745-0157.
Five million central venous catheters are inserted in patients in the United States every year. Even the most conservative estimates suggest that catheter-related sepsis will develop in at least 200,000 of these patients. Catheters are now the number one cause of bloodstream infections in patients with cancer and other critically ill patients. At least 25,000 patients die each year of catheter-related infection.

"Every two years we lose 50,000 patients, which is almost equivalent to the number of people we lost in Vietnam over a 10-year period," said Issam I. Raad, M.D., F.A.C.P., professor and chair ad interim of the Department of Infectious Diseases, Infection Control, and Employee Health at The University of Texas M.D. Anderson Cancer Center. "Twenty-five thousand people are dying every year of things that we put into their veins to try to help them."

The catheters, which allow repeated intravenous administration of medications, blood products, and chemotherapy without separate needle sticks, unfortunately also offer easy access for bacteria and fungi. The catheter connects the skin, which is a contaminated environment, with the bloodstream, which is supposed to be a sterile environment. Therein lies the danger.

"Catheters can get infected in different ways, but mainly, bugs that are on the skin migrate along the external surface, colonize the tip of the catheter, and invade the bloodstream," Dr. Raad said. "Or there's another route: From the hands of medical personnel, bugs can go through the hub, through the lumen, and invade the bloodstream." Either way, the result is often sepsis, which proves fatal in one of four intensive-care unit cases.

The number of patients becoming infected and dying is dropping quickly, though, as physicians around the world have begun using an antimicrobial catheter invented by Dr. Raad and a fellow researcher from Houston, Rabih O. Darouiche, M.D., a professor in the Department of Physical Medicine and Rehabilitation at Baylor College of Medicine. For their life-saving invention, Drs. Raad and Darouiche were honored this summer with the Outstanding Inventor of the Year Award 2004, presented by the Houston Intellectual Property Law Association.

Ten years ago, Drs. Raad and Darouiche decided that catheter-related infection was a problem waiting for a solution. Others had attempted to coat catheters with antibiotics, but their efforts fell short because the antimicrobial activity was too short-lived to help patients whose catheters might stay in place for 30 days or longer.

Rather than just coating the surface, Dr. Raad and his colleagues developed a method that allows antibiotics, specifically minocycline and rifampin, to permeate the plastic of the catheter, providing much more durable protection. "We use various ketones, like butyl acetate or acetone, mix the antibiotics with the acetone, and put the catheter in," said Dr. Raad. "The catheter swells because of the acetone and takes into its wall these two antibiotics." Cook Critical Care of Bloomington, Indiana, has licensed the technology and is now manufacturing the catheters.

In a study published in the New England Journal of Medicine in 1999, the investigators found that the rate of catheter-related sepsis dropped to nearly zero in patients with antibiotic-permeated catheters. "This is almost infection-proof," Dr. Raad said.

The U.S. Centers for Disease Control and Prevention issued guidelines in 2002 calling for the use of an antimicrobial central venous catheter in adults whose catheter is expected to remain in place for more than five days.

FOR MORE INFORMATION, contact Dr. Raad at (713) 792-7943.
How Cancer Happens and Ways to Lower Your Risk

A handful of genes may hold the secret to cancer’s mysteries. Genes reside within every cell in the human body and are made up of DNA, tiny pieces of code that control every aspect of a cell’s life: how much it can grow, what its primary functions are, how often it can divide to form new cells, and when it should die. Healthy cells turn into cancerous ones when their genes are damaged. This process, called carcinogenesis, occurs in three stages.

Stage 1: INITIATION
Although genes flawlessly control cellular functions in billions of cells throughout the human body, mistakes sometimes occur when DNA is copied from one cell to another, introducing a genetic error into all the cell’s offspring. These mistakes, or mutations, can happen spontaneously or be inherited, but often they result from cellular contact with cancer-causing agents, or carcinogens, such as tobacco, radiation, or viruses. Carcinogens can cause DNA strands to break easily or cause genes to become deleted, lined up in an incorrect order, or copied more times than necessary.

Normally, when DNA becomes damaged, there are genes in charge of repairing it so that the mistake cannot be passed on to new cells. If the DNA cannot be repaired, the cell commits suicide. However, if the genes that watch for and repair DNA damage are themselves damaged or destroyed, the normal defense mechanism is lost.

Stage 2: PROMOTION
One simple mutation by itself does not cause cancer; typically, cancer occurs when one mutation leads to other mutations that work together to defeat the growth regulation of a healthy cell. As new mutations occur, genes that control cell growth may start promoting cell growth when normally they would restrict it. As a result, the abnormal cells begin multiplying, often uncontrollably. In addition, as the genes that control cell death become altered, abnormal cells are able to stay alive when they should have committed suicide because their genetic material was damaged. These damaged cells are thus able to thrive and multiply, passing on their mistakes to future generations of cells.

Cells that acquire additional genetic changes that allow them to grow uncontrollably and avoid death have an advantage over normal cells.

Stage 3: PROGRESSION
Not all cancers form a tumor, but most do, and tumors take on a life of their own. Each tumor needs oxygen and nutrients from blood to survive, so tumors develop their own network of blood vessels that connect them to the rest of the body. This makes it possible for cancer to spread to other parts of the body; cancer cells that break loose from the original tumor can float through the bloodstream to other parts of the body where they attach themselves to healthy tissues. From there, they invade normal tissues, develop new blood vessels, and often overgrow normal tissues. These new cancer cells often have even more mutations than the cells in the original tumor, and as a result, the spreading cancer is usually harder to kill and, therefore, more deadly than the original tumor. Further, these new tumors may acquire more changes that allow them to resist normally effective treatments.

LOWERING YOUR CANCER RISK

Although scientists have learned a great deal about the role of genes in cancer development, they still have more to learn about the process and how to reverse it. In the meantime, you can cut down on your risk of cancer by following these health-smart tips:

1. Avoid tobacco products, including second-hand smoke, which contain many harmful chemicals that have been linked to lung, head and neck, and bladder cancers, among many others.
2. Avoid excessive unprotected exposure to ultraviolet rays from the sun, which are the leading cause of skin cancer.
3. Eat fried or grilled meats in moderation because these high-heat cooking processes can release harmful carcinogens in meats.
4. Consume lots of fruits and vegetables, which supply important vitamins and minerals for healthy cell development.
5. Exercise regularly to promote healthy body functions and control weight (obesity plays a role in many cancers).
6. Get regular medical checkups and screening tests for common cancers such as colon, prostate, breast, cervical, and skin cancers.

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

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

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Cancer-Related Neuroendocrine Dysfunction

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Neuroendocrine dysfunction is a major side effect of cancer and its treatment. Hormonal and metabolic abnormalities can profoundly affect the well-being of patients and even threaten their lives.

Often, neuroendocrine abnormalities last only as long as a particular treatment (e.g., exogenous hypercortisolism in patients treated with glucocorticoids). In other cases, the impact may be prolonged, either because an indolent tumor continues to contribute to certain abnormalities (e.g., hypercalcemia in some patients with islet cell tumors) or because the effects of the treatment may linger for several years (e.g., hypothalamic or pituitary dysfunction after cranial irradiation).

Some tumors are associated with paraneoplastic syndromes; ectopic hormone secretion, for example, may activate osteoclasts in the skeleton (resulting in hypercalcemia) or stimulate cortisol secretion from the adrenal glands (resulting in Cushing's syndrome). In other patients, antineoplastic therapy affects the normal function of endocrine glands and causes hormone deficiencies that increase morbidity and interfere with the patient's ability to tolerate cancer treatment. The early detection and correction of such side effects is needed to optimize patient outcomes.

Patients who have been treated with cranial irradiation, in particular, require prolonged surveillance because the deleterious effects of irradiation may not be apparent for many years. A comprehensive review of the patient's oncologic history is needed at the completion of therapy to design an appropriate surveillance strategy.

In children who have undergone cranial irradiation, growth should be monitored closely. For children who do not grow as expected, growth hormone replacement therapy is effective. In children eight to 10 years old, particular attention should focus on delayed or precocious puberty. In children with documented growth hormone or gonadal dysregulation, bone mineral density should also be evaluated.

In adults, detection of hypothalamic or pituitary abnormalities is more challenging. One strategy is to screen routinely for the integrity of the growth hormone axis (serum insulin-like growth factor-1 level) and the hypothalamic or pituitary gonadal axis (menstrual and sexual history or hormone levels). Physical examination should focus on signs of pituitary dysfunction such as loss of axillary or pubic hair, fine wrinkling of the skin, and adipose tissue redistribution. Advanced age and hypopituitarism are risk factors for osteoporosis in adults of either sex; thus, periodic bone mineral density measurement, nutritional counseling, and lifestyle education are very important.

Careful surveillance is particularly important because effective treatments are available for most neuroendocrine abnormalities.