Lab to clinic

Recurrent glioblastoma multiforme focus of clinical trial

Malignant brain tumors a new target for gene therapy

The prognosis for patients with glioblastoma multiforme, the most malignant of the primary brain tumors, is poor. Few patients with glioblastoma multiforme will be alive five years after the tumor is diagnosed. Standard therapies can temporarily shrink the tumor, relieving the intracranial pressure and its symptoms—headache, confusion, seizures, and loss of mental function. But patients who undergo these treatments, which include surgery, radiotherapy, and chemotherapy, may face uncomfortable complications or prolonged hospitalization. A new experimental treatment being offered patients with recurrent glioblastoma multiforme at The University of Texas M. D. Anderson Cancer Center may give hope for a longer or more comfortable life. The new treatment is called suicide gene therapy, and although it is experimental, the poor outcomes of current therapy for glioblastoma multiforme warrant its use.

“Glioblastoma multiforme poses a special clinical challenge,” said W. K. Alfred Yung, M.D., Deputy Chairman of the Department of Neuro-Oncology. “Although these tumors rarely metastasize to other parts of the body, they spread throughout the brain very widely, and the tumor boundaries are often indistinct. The standard treatments may eradicate or reduce the mass, but inevitably some of the remote tumor cells that have spread from the main tumor escape the therapy.” These residual tumor cells grow into new tumors: of the 11,000 to 12,000 patients treated for glioblastoma multiforme in the United States each year, most of them adults over the age of 50, nearly all will have a recurrence within a year after treatment of their first tumor.

Yung is principal investigator at M. D. Anderson for a multicenter clinical trial of suicide gene therapy. Working together on the study are a multidisciplinary team of neuro-oncologists, neurosurgeons, and neuroradiologists. Raymond Sawaya, M.D., Chairman of the Department of Neurosurgery, elaborated on the current therapy. “In some patients, surgery is not possible. When we do operate, we can usually remove the tumor, but even then we have not cured the patient, because many microscopic tumor cells remain. Nor does radiotherapy actually kill the tumor cells. The tumors are stopped for a while, but they soon start growing again. This is why we are looking for innovative alternative therapies.”

Therapy forces cells to kill themselves

Unlike gene therapies that correct a genetic aberration responsible for the cancer, the suicide gene strategy involves a gene that has nothing to do with human cancer, the *Herpes simplex* thymidine kinase gene. If properly inserted into human cancer cells, the gene changes the DNA of the cells so that they become susceptible to the antiviral drug ganciclovir.

To be effective, the suicide gene approach has to induce the patient’s tumor cells to express the *H. simplex* gene. The glioblastoma multiforme trial uses a retrovirus to introduce the gene into the cells, taking advantage of the retrovirus’s propensity to infect dividing cells. First the retrovirus is altered so it cannot replicate, and then the thymidine kinase gene is inserted into the retrovirus. The retrovirus is inserted into mouse fibroblast carriers, which are then suspended in a solution and injected into the tumor. Once inside the tumor, the fibroblasts divide and produce retroviruses, which infect the tumor cells, incorporating the thymidine kinase gene into the cell DNA.

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This approach has been used safely in human studies. The researchers expect that the gene therapy will reduce the size of the tumors with few of the side effects or discomforts of standard therapies. Because the fibroblasts come from mice, however, they may cause immune reactions in humans. The trial will measure both the effectiveness and the side effects of the gene constructs. To prevent exposure of normal noncancerous tissues to these constructs, the constructs are introduced directly into the tumors by a long needle.

**Stereotactic techniques pinpoint tumor location**

When an M. D. Anderson patient with inoperable, recurrent glioblastoma multiforme is identified and agrees to take part in the study, the neurosurgeon (usually Sawaya or Ian McCutcheon, M.D.) and neuroradiologist use stereotactic techniques to locate the tumor precisely in the brain. Stereotactic techniques were originally developed as a way of taking biopsies from the brain without opening the skull. The procedure is safe and widely used for performing biopsies, draining cysts, placing catheters, and administering drugs directly into the brain.

Sawaya recounted the procedure: “First, an external frame is positioned and securely fastened on the patient’s head; this is used as a reference to pinpoint the location of the tumor in the brain. Then a computed tomographic (CT) or magnetic resonance (MRI) scan of the brain shows the exact location of the tumor, including its margins, relative to the frame and calculates the optimal entry site. The frame serves as a means of guiding the needle to this site.” In the operating room, the site is prepared for the insertion of the needle through which the gene constructs are injected. “Only local anesthesia is used for the entire procedure—there is no pain,” continued Sawaya. “The beauty of this technique is that we know with certainty exactly where the tumor is without having to open the skull.”

Fourteen days after this treatment, the patient returns to the hospital for a 14-day course of ganciclovir. That is the end of the treatment. After that, said Yung, “we monitor the patient’s condition and the size of the tumor. About 30 patients have been treated on the study so far, only one of them at M. D. Anderson. That patient had some side effects, which were probably a reaction to a slight expansion of the brain caused by the introduction of the viral producer cells, a volume of approximately 10 milliliters. The effects resolved quickly, and we are now waiting to see the patient’s response.”

**Goal: local control with fewer side effects**

An early pilot study in about 15 patients showed that the suicide gene therapy concept is feasible. A private company now manufactures the gene constructs and is sponsoring the trial.

Will suicide gene therapy cure these “incurable” tumors? Probably not, said Sawaya. The ganciclovir will probably kill a portion of the tumor cells, but the residual cells will grow into another mass. “What we are offering,” he explained, “is an alternative that we expect will have an effect similar to that of the standard therapies, shrinking the tumor, buying some time for the patient. The advantage of gene therapy, we hope, is that the patient will be more comfortable and feel better.”

**Research focusing on refinements**

Yung and his colleagues have been conducting research in their laboratory that will allow them to try other gene therapy strategies in glioblastoma multiforme. One of these is the introduction of the normal (wild-type) p53 tumor suppressor gene into the tumor cells, whose mutated form allows tumor growth. However, the biggest barrier to cancer gene therapy right now is not the gene used, but the method used to deliver the gene into the cancer cells.

Many of the trials now on the drawing board will use an adenovirus rather than a retrovirus to introduce the gene. Although retroviruses were

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Advances in the treatment of cancer have led to improved cure rates and longer survival times, but many cancer patients still die of their disease. When the decision is made to end aggressive treatment and focus instead on relieving symptoms, patients and their caregivers must refocus the energy they have spent fighting the cancer on meeting new challenges.

A new guidebook published by the Supportive Cancer Care Network at The University of Texas M. D. Anderson Cancer Center is helping patients and their caregivers cope with both the emotional and the practical challenges of living with advanced cancer. *A Caring Community: Guidebook to Resources for Patients With Advanced Cancer and Their Caregivers* is the product of a two-year effort led by Anthony Greisinger, M.A., Cancer Prevention Project Specialist in the Department of Neuro-Oncology.

**Guidebook developed with help of patients**

In 1993, as part of the research for his doctoral dissertation in behavioral science, Greisinger began interviewing terminally ill cancer patients and their primary caregivers to identify their principal concerns. The purpose of these interviews was to gather information to develop a quality-of-life questionnaire for patients with advanced cancer.

Greisinger interviewed patients at M. D. Anderson Cancer Center and the Hospice of the Texas Medical Center and patients receiving home care from the Hospice. At the outset of each interview, he encouraged patients to talk about all areas of their lives that had been affected by cancer.

"Some of the patients had never been given the chance to talk about what they were going through," said Greisinger. "Patients really opened up and talked about the changes they had experienced as a result of the cancer. Many patients wanted to know how their experiences compared with those of other terminally ill patients—whether what they were experiencing was normal." During some of the interviews, Greisinger saw firsthand how difficult it can be for patients with advanced cancer to communicate with their families. "Sometimes the whole family would be in the room during an interview, and the patient would ask me ‘Do you think my family appreciates me? I’m not sure if they love me. I wish they would talk to me about the cancer but they won’t.’"

Greisinger also found that almost every patient and family asked for information about supportive care services. "Patients would ask me questions like ‘which legal documents do I need to complete? how do we choose a hospice; we’re scared—is it like a hospital? how do I get transportation?’ I was collecting information to create the quality-of-life scale, but this other need—for information about supportive care services—became obvious."

Greisinger decided to develop a resource guide to address patients’ concerns and highlight the services available to them in the community. "The patients were so helpful to me," he said. "When they realized that their participation in the study could help other patients, they offered me so much encouragement. I wanted to give something back to them, and what I could do was to collect what they had told me over the past year and put it together in a book."

Together with Stephanie Teleki, a research assistant in the Department of Community Oncology, Greisinger contacted agencies in Harris County to find out what specific services they provide to patients with advanced cancer. With the help of colleagues at M. D. Anderson, he wrote several sections about coping with advanced cancer, incorporating many of the insights patients had shared with him in over 200 interviews. Throughout the development of the guidebook, as he interviewed patients for his quality-of-life study, Greisinger would ask them to review drafts and offer suggestions. When the project was near completion, he did a pilot test to make sure that the guidebook was easy for patients to use and that it listed the information they needed. "It’s really the patients’ book," said Greisinger. "It’s a response to their needs and it is based on the insights they gave me to share with other patients."

**Specific, helpful information**

The guidebook is divided into two parts. Part I, "Coping With Advanced Cancer," addresses continued on page 4
Patients can play an active role in their care

“Many of the people I interview are unaware of the services that are available or become aware of them only in the last few weeks of life when they need hospice care,” said Greisinger. “My primary goal is to make patients aware of what is available in a more timely fashion.” Once patients know what is available, they can take a more active role in their own care.

“Sometimes patients with advanced cancer feel they’re losing control of their lives,” said Greisinger. “They need help with everyday activities like buying and preparing food, taking care of the house, and getting to the hospital. I think the book may make patients feel empowered. It helps them stay actively involved in improving their own quality of life.”

And, viewed from another perspective, the book helps patients stay actively involved in their community. Greisinger notes that patients with advanced cancer often feel isolated and cut off from the rest of the world. He decided to title the guidebook A Caring Community to emphasize that even though patients have advanced cancer, they are still valuable members of a community that cares about them.

Preparing for difficult decisions

When the time comes to plan for palliative care and to face end-of-life issues, many patients and their caregivers find it difficult to shift gears. “Often I talk to patients just before they are discharged from the hospital,” said Greisinger, “and they’ll say, ‘We’ve spent the last five years fighting the cancer, and now they’re telling us we should select a hospice, find a support group’—they’re just overwhelmed.” Greisinger hopes the new guidebook will alert patients to the decisions they may have to make and allow them more time to make those decisions.

In early 1996, M. D. Anderson discharge planning will become part of case management. Instead of working with a discharge planner right before they are discharged from the hospital, patients will work with the same case manager from the time of their first appointment through the end of their cancer care. Annette Bisanz, R.N., clinical nurse specialist in the Practice Outcomes Program, has been training the new case managers in discharge planning and has been giving each of them a copy of the book. She believes A Caring Community will help patients and their families prepare for tough decisions.

“This guidebook,” she said, “in a nutshell, helps patients face some of the things that they have to make decisions about. Even if the book just plants some good ideas, that will be useful. There’s nothing better than to work with an informed patient.”

Case managers, according to Bisanz, will give the book to patients and families when it appears that the cancer is not curable but before the patient’s condition has deteriorated so much that he or she is no longer able to actively participate in decision making. That way, patients and their families will have time to carefully consider and discuss their options for such things as hospice or nursing home...
care, support groups, medical equipment, transportation, and funeral planning and come to decisions based on the patient's wishes.

**Future editions planned**

The early response to the book has been positive. Within a month of the guidebook's initial printing in October 1995, over 4,000 of the 5,000 first-edition copies had been distributed. Almost every day, Greisinger receives requests for additional copies from agencies mentioned in the book and from social workers at other institutions.

Suggestions from patients and from physicians, nurses, and social workers will be incorporated into a revised edition of the guidebook planned for fall 1996. In the meantime, a second printing of the first edition is planned for spring 1996 to meet the demand for the book. Efforts are under way to adapt the guidebook for use in seven other metropolitan areas across the United States.

Greisinger is presently conducting the final phase of interviews for his quality-of-life study in advanced cancer patients. If a patient is from Harris County, Greisinger brings a copy of the guidebook to the interview and asks the patient and his or her caregivers to offer suggestions for future editions.

"The whole point of this project is to make the guidebook useful for patients and their caregivers," said Greisinger, "and when you are there in the room and they tell you that they needed something and they used the guidebook to find legal assistance or hospice information, or you realize that the guidebook helped them start to discuss a sensitive issue, it's a great feeling."

—**STEPHANIE P. DEMING**

Readers who would like more information may write Mr. Greisinger, Department of Neuro-Oncology, The University of Texas M. D. Anderson Cancer Center, Box 100, 1515 Holcombe Blvd., Houston, Texas 77030, or call (713) 792-7546.

**Glioblastoma multiforme**

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used first for gene therapy, adenoviruses appear to have many advantages. Whereas retroviruses must be permanently incorporated into each tumor cell's genome to produce the desired gene, adenoviruses can produce their proteins outside of the genome and thus need only take up temporary residency in the cell nucleus. Although the side effects of the viruses themselves are believed to be minimal, keeping the viral exposure brief reduces the risk of unwanted cell transformation by the introduced gene. The adenovirus can be injected in much higher concentrations to the tumor, so it is not necessary to insert it into carrier cells such as fibroblasts. Moreover, whereas retrovirus can infect only dividing cells, adenovirus can infect either dividing or nondividing cells, thus killing many more cells. This is especially critical in brain tumors, in which fewer than 10% of the cells are dividing at any moment.

Yung acknowledges that the fibroblast-retrovirus-gene construct is just a first step in the lengthy process of developing an effective clinical treatment. The next step is an improved delivery vehicle for the genetic construct—possibly adenovirus, possibly any of a number of other vehicles now under development. A longer term goal is a gene that can cure the cancer and a vehicle that can tell the difference between cancer cells and normal cells and infect only the cancer cells, "but we're nowhere near that level of sophistication yet," said Yung. "We have a large research program dedicated to finding a cure for glioblastoma multiforme, and we are one of the few clinical centers in the country with a comprehensive approach to these tumors. We are trying to find a way to give more hope and more life to patients with these tumors."

—**KATHRYN L. HALE**

**REFERRALS.** Physicians who would like to refer patients or patients interested in self-referral may write Dr. Yung at the Department of Neuro-Oncology (Box 100) or Dr. Sawaya at the Department of Neurosurgery (Box 64), The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, Texas 77030, or call (713) 794-1285 (Dr. Yung) or (713) 792-2400 (Dr. Sawaya). Physicians may also call the New Patient Referral office at (713) 792-6161 or (800) 392-1611.
Pituitary
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condition. For example, some symptoms of pituitary tumors mimic conditions related to diabetes, hyperlipidemia, and even primary hyperthyroidism. In these cases, the pituitary tumor may be diagnosed only after the onset of severe illness.

“The first challenge in managing pituitary tumors is confirming the diagnosis,” said Keith E. Friend, M.D., Endocrine Section, Department of Medical Specialties. Because of the location of pituitary tumors, advanced screening technologies such as radioimmunological assays, computed tomography, and magnetic resonance imaging are required to establish their biological makeup, exact position, and activity.

Some pituitary tumors never cause problems. Of those that do, some secrete an excess of certain hormones and others grow so large that they inhibit the normal function of the pituitary gland and impinge on other structures in the brain. Ectopic hormone production by tumors in other parts of the body can present an added challenge to diagnosing pituitary tumors. “Thorough endocrinological investigation is needed to determine precisely the type of tumor that has developed, and a series of biochemical tests are needed to determine with certainty if the excess hormones are being secreted from the pituitary gland or some other source,” Friend explained.

Two of the more common types of secretory tumors are prolactinomas, which secrete the hormone prolactin, and growth hormone (GH)-secreting tumors. These tumors come to clinical attention because of their widespread physiological and metabolic effects. Prolactinomas secrete excess prolactin, disrupting reproductive functioning in men and women. “Prolactinomas can stimulate the production of breast milk, cause abnormal menstrual cycles, and even lead to infertility,” Friend said. “In some cases, prolactinomas lead to impotence in men.”

Growth hormone–secreting tumors cause acromegaly, which is characterized by enlargement of distal parts of the body such as toes, fingers, feet, hands, nose, and ears. These tumors can also lead to arthritis and can increase the risk for gastrointestinal malignancies such as colon cancer. A common symptom of GH-secreting tumors is increased ring or shoe size. “These tumors are particularly insidious,” Friend explained. “What frequently happens is that a person with one of these tumors will meet a friend he has not seen for a while, years maybe, and the friend will notice changes in the person’s appearance. His facial features may be enlarged, for example. Quite often the changes have occurred so slowly that the people who live with the patient, his children or wife, will not have noticed any change.”

Other types of secretory tumors include adrenocorticotropin hormone (ACTH)–secreting tumors, which can lead to Cushing’s disease, and gonadotropin-secreting tumors, which can affect fertility. The small ACTH-secreting tumors can usually be detected only with highly sensitive screening. Gonadotropin-secreting tumors, on the other hand, are large and are usually detected once they impinge upon parts of the brain surrounding the pituitary gland.

Treatment: weighing the benefits and risks

Treatment presents the second challenge in the management of pituitary tumors. “Treatment recommendations are based on the tumor’s secretory status and its size,” said Friend. “We monitor some patients for several years, and unless hormone secretion levels or tumor size becomes threatening, treatment may not be required.”

There are two goals associated with the treatment of pituitary tumors. “The first,” said Friend, “is to lower the hormonal secretion level to a normal state, preserving pituitary function and reversing metabolic changes, such as abnormal growth in the case of GH-producing tumors. The other goal is to shrink or remove the tumor before it begins to affect other parts of the brain.” Treatment options include medications, surgery, radiotherapy, or a combination of surgery and radiotherapy.

When treatment is required, consideration must again be given to factors unique to pituitary tumors. “The pituitary gland is connected to the hypothalamus via the pituitary stalk,” said Friend. “The risk that the treatment, particularly surgery or radiotherapy, will cause further neurological damage warrants consideration.” Of primary consideration, although it is rare, is damage to the optic nerve because of its close proximity to the pituitary gland. “The clinician must decide if the disabilities caused by the tumor are sufficient to warrant the potential side effects of the treatment.”

Bromocriptine has been used to treat prolactinomas with a success rate of 80% to 90%. “The goal in treating this particular type of tumor is to inhibit the excess production of prolactin before
the onset of osteoporosis,” Friend reported. Depending on the size of the tumor, surgery may be the first line of treatment for GH-producing tumors; it has been effective in 50% of cases. “If surgery does not cure, the patient may be given octreotide or, in a small number of cases, bromocriptine to regulate hormone production. When medications are prescribed for either prolactinomas or GH-producing tumors, they usually must be taken for the rest of the patient’s life. Octreotide, for example, must be given by injection up to three times a day, although a long-acting preparation is under development.”

Treatment for pituitary tumors must be individualized to address specific symptoms and individual medical needs. “It is not uncommon for tumors to produce more than one hormone in excess. The most common combination is GH and prolactin,” explained Friend. So, the treatment chosen must be designed to adequately address both conditions. “In some cases, excess production of one hormone severely reduces production of another hormone. A loss in production of ACTH, for example, may lead to adrenal insufficiency, whereas a loss of gonadotropin hormones can cause reproductive abnormalities. These scenarios must be taken into consideration when the treatment is chosen.”

Accuracy, expertise key in managing pituitary tumors

Research on pituitary tumors is aimed at helping clinicians diagnose and treat these neoplasms. For example, M. D. Anderson was recently involved in testing the efficacy of octreotide in the treatment of GH-producing tumors. The cancer center is also serving as a regional center for a national acromegaly registry to evaluate various treatments. Friend said that M. D. Anderson is also directing interested patients to better prepare them and their family members to make decisions regarding care and to address the emotional and psychological impacts of this disease. “Although pituitary tumors are usually benign, they can cause serious illness that deeply affects the patient’s lifestyle and well-being. Early diagnosis and a sound treatment strategy are the keys to successful management of this disease.”

—VICKIE J. WILLIAMS

REFERRALS. Readers who would like more information may write Dr. Friend, Endocrine Section, Department of Medical Specialties, Box 15, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, Texas 77030, or call (713)792-2840. Those interested in referrals may call Dr. Friend or the New Patient Referral office, (713)792-6161 or (800)392-1611.

Pituitary Tumor Resources at M. D. Anderson Cancer Center

TUMORS AND SEQUELAE

Prolactinomas.................. Alternative therapies for bromocriptine resistance or intolerance
Acromegaly ...................... Regional center for national acromegaly registry
Cushing’s Disease ............ Specialized localization techniques, neuroradiology

SERVICES

Surgery ....................... Extensively experienced team led by Dr. Ian McCutcheon
Neuropathology ............... Immunohistochemical and electron microscopic tumor classification
Radiotherapy .................. Extensive experience in management of intracranial tumors
Location makes pituitary tumors difficult to diagnose and treat

Benign pituitary tumors threaten endocrine and nervous systems

Pituitary tumors, which arise at the base of the brain, account for up to 25% of all cancers within the cranium. Because of their obscure location and their slow growth, pituitary tumors present certain diagnostic and treatment challenges. Many pituitary tumors go unnoticed for years, and quite often they are discovered incidentally when the brain is imaged for another reason. Although pituitary tumors are usually benign, often by the time they are discovered they have caused severe hormonal imbalance or have invaded other parts of the cranium, compressing or injuring vital structures. Either can be debilitating. However, early detection, accurate diagnosis, and appropriate treatment can prevent this damage.

The University of Texas M. D. Anderson Cancer Center’s approach to managing pituitary tumors is to integrate expertise from many specialties, including endocrinology, neuroradiology, neurosurgery, pathology, and radiotherapy. This multidisciplinary team can expedite diagnoses and determine the most appropriate treatment.

Many variables complicate diagnosis

The first signs of pituitary tumors may not manifest for 10 years or more, but when they do appear they can be severe. Patients with these tumors may experience a wide range of complications, including headaches, visual disturbance, sexual or reproductive dysfunction, and discomfort or disfigurement caused by the enlargement of facial features and extremities. The exact complications will vary depending on the type of tumor and the presence of other health problems. Even after signs of the disease become a problem, they may not cause immediate alarm in the patient or the physician. Instead, the symptoms are often considered routine or isolated or are attributed to another