Treating Neurofibromatosis

Careful clinical intervention, long-term management, and promising research are key to limiting the devastating effects of this cancer-predisposition syndrome.

By Dawn Chalaire

[Name] has lived with neurofibromatosis type 1 (NF1) all of his life. He has undergone "at least 10" surgeries to remove or debulk some of the dozens of tumors growing on his body. He has endured stares, taunts, and worse from people because of the tumors that cover one side of his face. And he has watched family members struggle with the disease, including a [Name], who died of malignant NF1 3 years ago. NF1 can rob a person of many things, but in [Name] case, it has not broken his spirit.

"After my [Name] passed away," [Name] said, "I said that I didn't want any other family to go through what we went through. I also wanted people to understand. I would see people look at me, and I could tell that they wanted to know why I look like I do but were afraid to ask."

[Name] solution was to, with the help of his friend [Name], design a T-shirt with the words "Just Ask" on the front and a drawing of [Unreadable] on the back. [Name], who had always been reclusive because of his condition, started going with friends to sporting events, festivals, and restaurants wearing the shirt. People responded by approaching him and (Continued on page 2)
asking questions, which prompted patient to create a Web site for people with NF.

“We are reaching people from all over the globe on the Web site,” Patient said. “It is amazing how many visits we get from people who have NF or who have a family member with NF. They write and thank me for being their voice and helping them feel better about themselves and feel that they are not alone.”

The struggles and triumphs of life reflect the contradictory nature of NF1 itself. NF1 is the most common familial cancer predisposition syndrome, but most people have never heard of it and doctors often find it difficult to identify and diagnose. NF1 is a genetic disease that causes neurofibromas to grow on nerves at multiple sites in the body; half of all cases occur spontaneously. The clinical presentation of NF1 is extremely variable. Some patients have such mild symptoms that they don’t even know they have the disease, whereas others are afflicted with severe symptoms, such as facial disfigurements and spinal deformities that leave them wheelchair bound. Perhaps most troubling, NF1 is a chronic disease that can swiftly and disastrously become malignant. Although neurofibromas are benign, patients with NF1 have an 8%-13% lifetime risk of developing malignant peripheral nerve sheath tumors, which carry a 5-year survival rate of less than 50%.

It is a confounding reality that NF specialists at The University of Texas M. D. Anderson Cancer Center navigate daily. As their patients face the disease’s unfolding consequences—which are all too often physically, emotionally, and psychologically devastating—deciding how and when to treat them becomes a lifetime challenge.

**Genetic basis of NF1 and associated symptoms**

John Slopis, M.D., recently spent the better part of an afternoon explaining the complex nature of NF and its often devastating effects on individuals and families. “It’s a fascinating disorder,” said Dr. Slopis, an associate professor in the

caused by three separate genetic mutations. NF1 is by far the most common of the three disorders, with a birth incidence of 1 in 2500. (Please see sidebar on page 3 for more information about NF2 and schwannomatosis.)

The variability of NF1 symptoms and their severity can be explained in part by the nature of the NF1 gene. The gene is expressed in the second or third week of embryological development, plays a central role in the normal development of almost all tissues, and is present in just about every cell. It is localized to a very broad area on chromosome 17, and DNA mutational analyses have revealed well over 1,000 different mutation patterns within this chromosome.

“There appear to be hot spots that are critical within the gene for these clinical syndromes,” Dr. Slopis said, “but because of the variability, some patients will have skin problems, some will have bone problems, some will have malignancies, and some will have only benign disease. And if you look at the clinical symptoms associated with NF1, it’s a long list, and you wonder what is similar about all these people.”

Patients with NF1 face a lifetime of health problems. The most common manifestation of the disease is the occurrence of multiple benign nerve tumors called neurofibromas. The number and size of these tumors vary widely; in most patients their effects are mild to moderate, but some patients have literally thousands of them. Most of these benign tumors do not require treatment, but surgical, orthopedic, or endocrine interventions become necessary if the tumors threaten or affect critical structures or

---

**The most important thing is to recognize the signs and symptoms of malignancy as soon as possible and, if possible, to resect the tumor.**

— Dr. John Slopis
Rarer Types of Neurofibromatosis

The other two types of neurofibromatosis—neurofibromatosis type 2 (NF2) and schwannomatosis—are much rarer than NF1. Until recently, schwannomatosis was thought to be a variant of NF2. In both conditions, the most common nerve-associated tumors are schwannomas, which develop in the Schwann cells that help form the myelin sheath covering nerves.

NF2 is characterized by the slow growth of tumors on the eighth cranial nerve, which is important for both hearing and balance. The tumors can grow so large that they damage the brain stem, which can cause serious disability. Schwannomas can also occur along any other nerve in the body and are often seen as bumps under the skin. People with NF2 are at a higher risk for other types of central nervous system tumors, including meningiomas and ependymomas.

“People with NF2 have problems with deafness and facial paralysis, weakness in the arms and legs, and spinal cord compression,” said John Slopis, M.D., an associate professor in the Department of Neuro-Oncology and director of the Neurofibromatosis Clinic at M.D. Anderson Cancer Center. “NF2 is in most cases relentless; it’s a horrible, crippling disease.”

NF2 tumors are often surgically removed to preserve function and relieve symptoms, but such surgeries are risky and sometimes impossible when the tumors are located too close to critical structures. Dr. Slopis and Dr. Ian McCutcheon, a professor in the Department of Neurosurgery, are collaborating with Razelle Kurzrock, M.D., professor and chair of the Department of Investigational Cancer Therapeutics, who is leading phase I clinical trials investigating the use of various targeted agents for the treatment of NF2 tumors.

Schwannomatosis is distinguished by the development of multiple schwannomas anywhere in the body except on the vestibular nerve. The number of tumors varies, with about a third of patients having tumors that are limited to a particular body part, such as an arm or leg.

The main symptom of schwannomatosis is pain, which can be so severe that it is disabling. Medications and surgery are used to treat the pain, which is usually caused by a schwannoma that enlarges and compresses a nerve or puts pressure on adjacent tissues. As in NF1, nerve-sparking surgery is often possible in schwannomatosis. However, there is no accepted standard treatment for schwannomatosis.

Specialized care for patients with NF

The M. D. Anderson Cancer Center NF Clinic is one of only about six specialized multidisciplinary clinics for NF patients in the United States. Upon their first visit to the NF Clinic, patients undergo a thorough medical history, physical evaluation, and imaging studies. All new patients are assessed clinically to confirm the diagnosis of NF1. Blood samples for DNA testing can confirm the presence of the NF1 gene. Biopsy is not necessary for the diagnosis of NF, and in fact, needle biopsy of NF tumors can be very painful.

“After diagnosis, we talk with the patients and determine the severity of their clinical symptoms,” said Dr. Slopis. “We try to create, basically, a profile for that individual. And that profile then becomes the platform for their long-term care projection. In other words, what are the issues that we really need to worry about?”

After their initial consultation, patients return for follow-up on a regular basis to check for disease progression, worsening of symptoms, and signs that a previously benign tumor is becoming malignant. “The most important thing is to recognize the signs and symptoms of malignancy as soon as possible and, if possible, to resect the tumor,” Dr. Slopis said. “It takes a fair amount of practice to identify malignant transformation.”

The most common symptoms of this transformation are the patient’s sensation that something is growing rapidly inside, rapid development of neurologic and/or focal deficits, and relentless localized pain. Magnetic resonance imaging is then used to determine whether the tumor in question is growing. A study currently under way at M. D. Anderson, led by Dr. McCutcheon and Dr. Slopis, is evaluating the use of positron emission tomography/computed tomography imaging to identify tumors in the early stages of malignant transformation.

Another study, funded this year by the Texas Neurofibromatosis Foundation for whole-gene sequencing of the NF1 gene, will allow a genotype-phenotype correlation in malignant peripheral nerve sheath tumors. The hope is to identify specific mutations that portend the ultimate development of malignancy in a given patient with NF1.

(Continued on page 4)
Treating Neurofibromatosis

(Continued from page 3)

Treatment of malignant peripheral nerve sheath tumors

Spotting malignant transformation early is important because the successful removal of malignant peripheral nerve sheath tumors is a patient’s best chance for a cure. The more time a tumor has to grow, the more difficult it becomes to remove it and the more likely it is to metastasize. “What we tell patients is that you have to pick your battles, and so we define what’s worth doing battle over,” said Dr. McCutcheon.

Before attempting to remove a tumor encircling a nerve, Dr. McCutcheon and his team first use electrical stimulation to identify the affected nerve, which, depending on the importance of the nerve, helps them to decide how aggressively to approach the tumor. To the untrained eye, removing a peripheral nerve sheath tumor without severely damaging the nerve seems impossible. “When you look at a tumor on a scan or even during surgery, it looks like the nerve goes in one end of the tumor and comes out the other end,” Dr. McCutcheon said. “So inside the tumor there’s going to be all these bits of the nerve, and how are you going to take it out? But the reality is that in probably 90% of these operations, there is a single fascicle going in and coming out of the tumor, and all the other parts of the nerve are going around the outside of the tumor. So you can actually separate the tumor from the nerve and preserve the great majority of the intact, functional portion of the nerve.”

In a few cases, Dr. McCutcheon has been able to spare more than a patient’s nerve. “We’ve actually had people come to us who have been told elsewhere that they needed to have an operation for a tumor in their leg but that it had to be an amputation,” he said, “and they were not even being considered for some kind of surgery where you spare the nerve and thus preserve the leg.”

In addition to sparing the nerve, the other goal of surgery for malignant peripheral nerve sheath tumors is to remove the tumor with a clear margin of normal tissue around it. If the tumor is removed without clear margins, the patient is referred to the Sarcoma Center for treatment of the residual tumor, typically with ifosfamide-based chemotherapy, with or without radiation therapy.

M. D. Anderson specialists recently began collaborating with oncologists at Johns Hopkins Hospital to determine how radical an operation must be for malignant peripheral nerve sheath tumors to achieve optimal tumor control and patient survival. Researchers at M. D. Anderson are also attempting to characterize the tumor genetics and signaling mechanisms of NF1 and NF2 in the hope that their findings will lead to more targeted systemic therapies. A recent study led by Dina Lev, M.D., an assistant professor in the Department of Cancer Biology, identified both AKT and mammalian target of rapamycin as potential targets for the treatment of malignant peripheral nerve sheath tumors. Drs. Slopis and McCutcheon are developing a high-resolution chemotherapy trial to analyze NF tumor tissues before and after chemotherapy to determine the molecular changes involved in transformation and response or resistance to therapy.

Social and cognitive needs of patients with NF

Because NF is a chronic disease that requires long-term management and follow-up, the NF Clinic at M. D. Anderson accepts adult patients. Most of the adult patients, which now make up a third of the clinic’s patients, have been treated in the NF Clinic since childhood. Consequently, Dr. Slopis knows most of the patients and their families very well and spends a good deal of his time informally counseling them, answering their questions, and writing letters or filling out various forms for them.

“All of the patients have great things to say about Dr. Slopis,” said who has been coming to M. D. Anderson for treatment and follow-up since 1978. “He always takes time to answer all your questions and explain everything to you.”

Dr. Slopis, in turn, calls “a very active, very cool guy. He lobbies...
IN BRIEF

Bladder Cancer Study Elucidates Disease’s Genetic Causes

Each year, bladder cancer is diagnosed in about 70,980 Americans and kills about 14,330. It’s known that smoking and occupational exposure to diesel fumes increase the risk of bladder cancer, as does genetic predisposition, which appears to account for around a third of cases. First-degree relatives of people with bladder cancer have at least a 50% greater risk of developing the disease than the general population. Unfortunately, screening techniques and chemopreventive agents for people at risk of developing inherited bladder cancer are lacking. But a recent international study led by M. D. Anderson researchers might help change that.

It had been suggested previously that urine tests for prostate stem cell antigen (PSCA) could help screen for bladder cancer, and the recent study, published in *Nature Genetics*, pinpoints a PSCA genetic variation that raises a man’s risk of bladder cancer by 30%-40%. PSCA is an established marker for the presence and severity of prostate cancer, and while researchers have long thought that PSCA may play a role in bladder cancer, there was little evidence.

The PSCA variation resides in what might be termed a bad neighborhood of the genome. “The neighboring genomic region has been identified previously as a possible problem for breast, prostate, colorectal, and bladder cancer, but we didn’t know why,” said lead author Xifeng Wu, M.D., Ph.D., a professor in the Department of Epidemiology. “With this research, we were able to find a novel specific gene and a functional variation that are independent of the previous suspects. We found a ‘why’ to many of the questions about genetic causes of bladder cancer.”

Researchers compared 969 bladder cancer patients with 954 healthy controls using whole genome analysis in the discovery phase. They then replicated the finding in 12 other groups in the United States and Europe involving a total of 6,667 patients and 39,590 healthy individuals. Dr. Wu and her team found that PSCA gene missense variation rs2294008 raised the risk of bladder cancer.

The next step is taking the findings from the bench to the bedside. “When we’ve identified all the genes that are linked to bladder cancer, we plan to develop a Web-based tool so physicians can calculate accurately and easily a patient’s risk of getting the disease,” Dr. Wu said. Such an innovation could mean new hope against this deadly disease. “Early identification of risk may help save lives with chemoprevention or early treatment.”

New Radiation Therapy Approach for Limited Small Cell Lung Cancer Reduces Esophagitis

An important problem in the treatment of small cell lung cancer with radiation therapy is how to maximize benefit while avoiding severe inflammation of the esophagus. Recently, researchers tested a new method of accelerated radiation therapy that appears to provide good local control while minimizing esophageal inflammation, or esophagitis.

The study built upon previous work in limited-stage small cell lung cancer, which kills more than 7,500 Americans a year. “We have made significant progress in the treatment of this disease by combining chemotherapy with thoracic radiation therapy and prophylactic cranial therapy,” said lead author Ritsuko Komaki, M.D., professor and program director of Lung Cancer Research and Thoracic Radiation Oncology in M. D. Anderson’s Division of Radiation Oncology. “However, the 5-year overall survival rate among patients diagnosed with earlier-stage disease is still only 26%.”

Improved overall survival rates were seen in a phase III clinical study involving patients with small cell lung cancer in one lung and possibly lymph nodes but not at distant sites. The patients received chemotherapy plus accelerated fractionated radiation therapy, in which radiation doses were increased over time. However, this approach resulted in a higher incidence of acute esophagitis, so researchers designed a phase II study to try another way of delivering the radiation.

In the new study, patients received a less-accelerated schedule of radiation therapy over three weeks, followed by two weeks of higher-dose radiation. “The last two weeks of treatment are when radiation-resistant cancer cells often start to proliferate, which is why we gave the patients a boost of radiation twice a day during that period,” Dr. Komaki said.

During a median follow-up time of 19 months, local tumor control was observed in 90% of patients—41% experienced a complete response, and 39% had a partial response. Additionally, the rate of acute esophagitis (18% of patients) was significantly lower than the rate in the previous study (27%). Even though long-term overall survival did not increase, the other results were encouraging, Dr. Komaki said. “This research is important because we achieved a high level of disease control while minimizing damage to the esophagus,” she explained.

Dr. Komaki, who holds the Gloria Lupton Tennison Distinguished Professorship in Lung Cancer Research at M. D. Anderson, said further investigation is needed. Future study may include a cycle of induction chemotherapy before the concurrent chemotherapy and radiation therapy. Improved systemic treatment and staging work-ups are also needed, Dr. Komaki said.

Results were presented in November in an oral session at the annual meeting of the American Society for Radiation Oncology.
Personalized Therapy for Lung Cancer

Investigators are developing tumor profiles in hopes of matching each patient with the best treatment protocol.

By Joe Munch

The outlook for many lung cancer patients remains dismal, in part because more than half initially present with advanced, hard-to-treat metastatic disease. Chemotherapy provides a limited survival benefit, and most second-line therapies work for only a few patients.

However, there may be a new hope on the horizon for patients with advanced non–small cell lung cancer (NSCLC), a collection of tumor types that comprise the majority of lung cancers. The first stage of a study aimed at identifying biomarkers that predict NSCLC’s susceptibility to certain therapeutic agents is nearing completion. Findings from this study should some day enable M. D. Anderson researchers to provide NSCLC patients with personalized therapy using drugs that block the tumor’s activity based on its specific molecular profile.

“We already know that cytotoxic chemotherapy improves survival in advanced lung cancer patients a little. The next step in improving survival is to personalize treatment from the very beginning using molecularly targeted agents,” said Roy Herbst, M.D., Ph.D., professor and chief of the Section of Thoracic Medical Oncology at M. D. Anderson. “We’re moving toward an era in which we would like to be able to profile any patient’s tumor and use that information to treat them in a more effective and less toxic way.”

We would like to be able to profile any patient’s tumor and use that information to treat them in a more effective and less toxic way.”
— Dr. Roy Herbst

The tumor specimens are analyzed for 11 biomarkers related to four key molecular pathways believed to be essential in NSCLC. The molecular profiling process also includes examining tumor specimens for undiscovered molecular changes that could eventually serve as therapeutic targets or therapy-response biomarkers.

Eligible patients are then assigned to one of four phase II clinical trials though adaptive randomization, in which information on patients enrolled at the beginning of the study influences the treatment choice for patients enrolled later in the study. Each of the phase II trials is testing a molecularly targeted agent or agents—sorafenib, vandetanib, erlotinib, or erlotinib plus bexarotene—all of which have been shown to act against lung cancer. Response to therapy is monitored in part to assess the effectiveness of treatment assignments based on the biomarkers. The data will also help investigators decide which combinations of drugs will be used in BATTLE II, the next generation of this program, in which combinations of agents will be used to overcome drug resistance mechanisms.

While the analyzed results of BATTLE I are not yet available, the study has generated data that are helping to elucidate the characteristics and molecular pathways of tumorigenesis. “With this knowledge, we hope to be able to look at a tumor or even a blood sample and understand the factors that are causing the tumor to proliferate—the essential malignant functions of the tumor—and then try to target those components more specifically to prevent the tumor from growing,” Dr. Herbst said.

Added Ignacio Wistuba, M.D., a professor in the Department of Pathology and director of the Thoracic Molecular Pathology Laboratory: “If any of the molecular markers tested or discovered in BATTLE are shown to predict a better response to a particular molecularly targeted therapy, those markers could be translated into standard clinical practice, pending the therapies’ validation in larger clinical trials.”

One of the drugs used in a BATTLE trial, vandetanib, has already shown benefit in NSCLC. Vandetanib inhibits both the epidermal growth factor receptor and the vascular endothelial growth factor receptor, which are believed to fuel the growth of some NSCLCs when functioning abnormally. In a separate study, Dr. Herbst and a team of international investigators found that NSCLC patients treated with vandetanib plus docetaxel, a standard chemotherapy agent, had a longer progression-free survival duration than patients treated

(Continued on page 8)
Genetic Screening for Cancer Risks Gives Patients Options

In the past, people with a family history of cancer had few options other than worrying and waiting to see if they developed the disease. But today, the relatively new science of genetic testing can let people more accurately determine their risk for some hereditary cancers and better understand their options.

Hereditary syndromes

About 5%–10% of cancers are the result of inherited genetic mutations that are passed from one generation to the next. These mutations cause what are called hereditary cancer predisposition syndromes. Not all mutations involved in hereditary cancer predisposition syndromes have been identified, but some can be detected by blood tests:

- **Cowden syndrome**, which is characterized by small, noncancerous growths (called hamartomas) on the skin and mucous membranes. People with Cowden syndrome also have an increased risk of tumors developing in the breast, uterus, and thyroid. Cowden syndrome is caused by a mutation of the PTEN gene, which controls the production of an enzyme that regulates cell growth. Mutations of this gene cause uncontrolled cell growth that results in benign or malignant tumors.

- Other hereditary cancer predisposition syndromes include neurofibromatosis (leading to malignant nerve sheath tumors), Gardner’s syndrome (leading to cancer of the gastrointestinal tract), Li-Fraumeni syndrome (leading to multiple types of cancer), and Von Hippel-Lindau disease (leading to cancers of the eye, brain, and spinal cord). Although not all individuals with an inherited mutation develop cancer, they do face a significantly increased risk of developing cancer.

Genetic testing

“In a woman who does not have cancer but who tests positive for a BRCA mutation, the lifetime risk of developing breast cancer is 80% and the risk of ovarian cancer is 50%,” said Banu Arun, M.D., an associate professor in the Department of Breast Medical Oncology and co-director of the Clinical Cancer Genetics Program at M. D. Anderson Cancer Center.

The most effective strategy to determine whether a family has a hereditary genetic mutation is to test a family member who has cancer, Dr. Arun said. “For example, if a woman tells us her mother had breast cancer at age 35 and is now 60, we would test the mother,” she said. “If she has the mutation, then we would want to test the daughter. If the mother doesn’t have the mutation, then we would not test the daughter.”

A person who doesn’t have cancer but who does have a hereditary mutation can take a more proactive approach to cancer screening. For example, a person with Lynch syndrome would need to have screening colonoscopies at regular intervals to detect and remove precancerous polyps.

Dr. Arun said some patients can also consider preventive surgery. For example, a bilateral mastectomy (removal of both breasts) reduces the risk of breast cancer by about 95%.

Genetic counseling

Deciding whether to be tested for an inherited cancer-causing genetic mutation can be difficult. In addition to possibly causing a psychologic burden, testing is expensive and may not be covered by insurance.

To guide patients through their decisions, M. D. Anderson’s Clinical Cancer Genetics Program offers extensive pre- and post-testing genetic counseling. “We give counseling and explain what the positive or negative results of testing mean,” said Dr. Arun. “It’s easier to explain a positive test result because it means you have a mutation. However, a negative test result could mean that there is no mutation or that there’s still something going on in the family but we don’t know which gene is involved.”

For more information, talk to your physician, or visit the Clinical Cancer Genetics Program online at www.mdanderson.org/departments/ccg.

OncoLog, November/December 2009
B. Tutt

©2009 The University of Texas M. D. Anderson Cancer Center
Treating Neurofibromatosis
(Continued from page 4)

in Washington, organizes lectures, and travels around the state to talk about NF.”

“It has many friends and seems to have found a way to avoid the severe social isolation that often goes along with having NF.

“NF1 has an impact on how those affected relate to other people and on how other people relate to them,” Dr. Slopis
said. “And that speaks to the cognitive and behavioral features of NF1 because of the impact of the gene on brain development.”

Many children with NF1 will have clinically defined attention deficit hyperactivity disorder, and 40% will have dyslexia. At the M. D. Anderson NF Clinic, such patients are referred to Bartlett Moore, Ph.D., a pediatric neuropsychologist in the Division of Pediatrics, to help them cope with their learning disabilities. “It appears to be a huge problem that creates this sort of socioeconomic decline in the population. Many do so badly in their educational efforts that they don’t finish school. You can imagine the effect this would have on multiple generations of a family with NF,” Dr. Slopis said.

But with the help of specialized, multidisciplinary clinics such as the one at M. D. Anderson—and clinicians such as Dr. Slopis and Dr. McCutcheon—the vicious cycle of NF can be broken.

For more information, call Dr. Slopis at 713-563-1372 or Dr. McCutcheon at 713-563-8706.

Personalized Therapy for Lung Cancer
(Continued from page 6)

with docetaxel alone and an improvement in their disease-related symptoms. While the separate studies’ results showed the promise of using targeted therapies to treat lung cancer, the ultimate goal of targeted therapies may be to eliminate the need for chemotherapy altogether in patients whose tumor characteristics indicate that foregoing chemotherapy is appropriate.

“Right now, most patients who are diagnosed with lung cancer receive chemotherapy. So even if patients also get these new, targeted agents, many still have to cope with all the toxicity of the chemotherapy, and that affects their quality of life,” Dr. Herbst said. “My hope would be that someday we will be using these targeted agents in the absence of chemotherapy. We’ll see each patient being treated early on with the drug or drug combination that is going to be the most beneficial based on the actual genotype of the tumor.”

For more information, contact Dr. Herbst at 713-792-6363 or Dr. Wistuba at 713-563-9184.