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The New York Times

Science Times

TUESDAY, NOVEMBER 17, 2009

Breaching a Barrier to Fight Brain Cancer

By DENISE GRADY

Dr. Howard Riina threaded a slender tube through a maze of arteries in Dennis Sugrue's brain, watching X-ray images on a monitor to track his progress. At the site where a previous operation had removed a malignant tumor, he infused a drug called mannitol and unleashed a flood of the cancer drug Avastin.

Doctors and nurses watched intently, worried that the Avastin could cause brain swelling, a hemorrhage or a seizure. But Mr. Sugrue emerged unscathed. A half hour after the procedure, he woke up from anesthesia mumbling, "More is better," and wishing aloud that he could have had a bigger dose.

It was an experiment. Mr. Sugrue, 50, who works for a hedge fund and has two teenage children, was in a study for people with glioblastoma — the same type of brain tumor that killed Senator Edward M. Kennedy of Massachusetts in August — and was only the second person ever to have Avastin sprayed directly into his brain.

Getting drugs into the brain has always been a major challenge in treating tumors and other neurological diseases, because the blood-brain barrier, a natural defense system, keeps many drugs out. The study that Mr. Sugrue is in, at NewYork-Presbyterian/Weill Cornell, combines old technologies in a new way to open the barrier and deliver extraordinarily high doses of Avastin straight to these deadly tumors — without soaking the rest of the brain in the drug and exposing it to side effects.

The goal is to find better ways to treat glioblastomas. But the technique might also be useful for brain metastases, meaning cancer that has spread from other parts of the body, like the breasts or lungs — something that occurs in about 100,000 people a year in the United States. The same procedure could also deliver other drugs and might eventually be used to treat neurological disorders like multiple



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TREATMENT *Dr. Howard Riina looking at X-rays during a procedure performed on Dennis Sugrue, 50, who has glioblastoma, the cancer that Senator Edward M. Kennedy of Massachusetts had.*

sclerosis or Parkinson's disease, if suitable therapies are developed.

The defense system that doctors are trying to breach evolved to keep out toxins and microbes. It consists mainly of cells that line the walls of capillaries in the brain and are so tightly packed that many molecules in the bloodstream cannot slip out between cells to reach the brain tissue itself. But certain drugs, like mannitol, will temporarily open the barrier and were first used more than 20 years ago to help other medicines reach the brain.

The new technique refines the art of opening the barrier: it uses micro-catheters — fine, highly flexible tubes that

are inserted into an artery in the groin and then threaded up into tiny blood vessels nearly anywhere in the brain — to spray chemotherapy directly onto tumors or areas from which they have been removed. The catheters are normally used to deliver clot-dissolving drugs to the brain to treat strokes.

"This will substantially alter the way that chemotherapy is given in the future," said Dr. John Boockvar, the brain surgeon who devised the trial. "But we have to prove that at certain doses, nobody gets hurt."

Referring to glioblastoma patients, Dr. Riina said, "Everyone is looking for some-



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PREPARATION Dennis Sugrue, of Stamford, Conn., had staples removed before undergoing a procedure in which the cancer drug Avastin was injected into his brain.

thing to do for these people.”

“Even if you buy someone just a year, that could be a wedding or a graduation,” he continued. “You never know what might happen in the year they hold onto.”

The study, which began in August, is still in its earliest phase, meaning its main goal is to measure safety, not efficacy — to find out if it is safe to spray Avastin directly into brain arteries and at what dose. Nonetheless, the doctors were pleased when M.R.I. scans of the first few patients showed that the treatment seemed to erase any sign of recurring glioblastomas. But how long the effect will last remains to be seen.

“A beautiful M.R.I. scan doesn’t mean it’s cured,” Dr. Boockvar said.

Despite a beautiful scan, the first patient who was treated died in October, from pneumonia and the spread of glioblastoma to his brainstem.

Innovations are desperately needed to make headway against glioblastoma, which is “one of the most deadly tumors that exist in humans,” said Dr. Russell Lonser, chairman of surgical neurology at the National Institutes of Health.

“This is a very good start,” Dr. Lonser said. “The early data is very interesting and exciting.”

The complexity of a study like this goes beyond the science. Clinical trials are also a complicated pact, emotionally and ethically, between desperate patients and doctors who must balance their ambition as researchers against their duty as clinicians, and must walk a fine line between offering too much hope and not enough.

“I tell patients, ‘I’m going to try to cure your disease, but so far glioblastoma is an incurable disease,’” Dr. Boockvar said.

Extending Life

“I’m optimistic,” Mr. Sugrue said one morning in September, after scheduling a second brain operation. But he had tears in his eyes.

There are about 10,000 new cases of glioblastoma a year in the United States, mostly in people over 45. The tumors are notorious for growing back like weeds even after being cut out and

blasted with chemotherapy and radiation, and they are nearly always fatal. With the best treatment, the median survival time is about 15 months.

But in the last five years, the number of patients who survive 2 years has increased to 25 percent, from 8 percent, largely because doctors began using a chemotherapy pill called temozolomide, or Temodar, along with radiation (Temodar is believed to seep through the blood-brain barrier).

Dr. Boockvar said he thought that if he could just keep patients alive for two years, more advances might come along and give them time.

“The glioblastoma population is very studyable, unfortunately, because the prognosis is so grim,” he said.

Patients often wind up on the front lines of research, figuring they have little to lose and hoping they will be lucky enough to test the big breakthrough. More than 500 studies for people with glioblastoma are listed on the government Web site www.clinicaltrials.gov.

Mr. Sugrue, who lives in Stamford, Conn., with his wife, Donna, and their chil-

dren Molly and Tim, began having headaches in April. He thought he had a sinus problem. But a scan found a brain tumor nearly the size of a golf ball. A local doctor referred him to Dr. Boockvar. He had the standard treatment: surgery, temozolomide pills and six weeks of radiation, which ended on June 25.

In an experimental technique for glioblastoma, drugs are sprayed directly on the tumor.

By July, an ominous bright spot on his M.R.I. scan suggested that the tumor might already be growing back. He continued chemotherapy, but the spot kept enlarging.

By mid-September, the Sugrues were back in Dr. Boockvar’s office to plan their next step. Stubby hair was growing in on Mr. Sugrue’s scalp, except for a bare patch, around an arcing scar above his right ear. His eyes, bright blue with thick, dark lashes that gave him a boyish look, searched the doctor’s face.

The headaches had returned. New scans, displayed on a computer screen, showed signs of brain swelling and bright spots that should not have been there. Dr. Boockvar recommended more surgery and then chemotherapy with Avastin, which had recently been approved for recurring glioblastoma.

It was approved for intravenous use — to be dripped into a vein, usually in the arm — but he said Mr. Sugrue would be an ideal candidate for his study, in which the drug would be infused directly into an artery in the brain, producing levels at least 50 times what the intravenous route could achieve. One other patient had been treated that way, and M.R.I. scans showed that recurring tumors seemed to have melted away.

Mr. Sugrue said he was all for it, even though Dr. Boockvar warned him that the drug was no magic bullet. Then Dr. Boockvar ticked off the risks from a second brain operation.

“I have to quote you a 5 percent risk you’ll be visibly weak,” he said. “A 1 percent chance of paralysis on the left side.”

Mr. Sugrue wiped his eyes and began to apologize for losing his composure, but the surgeon cut him off and said, “In neurosurgery they say that if you don’t make your patient cry, you haven’t gotten informed consent.”

The trial grew out of a conversation about a year ago between Dr. Boockvar and Dr. Riina, an expert in using microcatheters to treat strokes.

“I said, ‘Why can’t you infuse chemotherapy for my brain tumor patients?’” Dr. Boockvar recalled. “And he said: ‘I can.



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CHEMOTHERAPY Dr. John Boockvar, left, watched as Dr. Howard Riina and Jared Knopman injected drugs into Mr. Sugrue's skull. The technique uses microcatheters.

Just show me what you want to do.'"

Dr. Riina said, "Technically, I can go anywhere in your brain."

He said microcatheter technology had advanced "light-years" in the last decade and was just waiting for a new drug to come along for glioblastoma.

Offering just a shadow of hope for those with an incurable disease.

They wrote up a plan to test what they called "superselective intra-arterial cerebral infusion" of Avastin in 30 patients with glioblastomas that had recurred after standard treatment. Each patient would receive just one treatment directed into the brain, followed weeks later by a series of intravenous treatments with Avastin.

Their study involves a technique first developed about 30 years ago, which uses mannitol to open the blood-brain barrier

temporarily to get chemotherapy into the brain. Mannitol pulls water out of the tightly packed cells lining the capillaries so that they shrink and pull away from one another, opening up gaps through which drug molecules can pass into the brain.

The technique was developed by Dr. Edward A. Neuwelt, a neurosurgeon at Oregon Health Sciences University and the Veterans Affairs Hospital in Portland. Its best results have been in people with a rare type of brain tumor called a primary central nervous system lymphoma. But it has not been helpful with glioblastoma, because until recently there was no chemotherapy to infuse that would have much effect on those tumors.

Dr. Neuwelt said that Avastin had helped to renew interest in opening the blood-brain barrier but that researchers disagreed about whether the drug would lend itself to that use.

Avastin starves tumors by blocking the growth of new blood vessels, which they need to survive. Dr. Boockvar said microcatheters should increase the odds of success by delivering a high dose of the drug directly to where it was needed most. Earlier research with other drugs used larger

catheters inserted into the carotid arteries, which feed the entire brain — meaning that the tumor did not receive the most concentrated dose and that healthy brain tissue was exposed to the toxic drugs.

By mid-November, the researchers had treated five patients, including Mr. Sugrue; they first infused mannitol, waited five minutes and then sprayed in the Avastin. In all the patients' M.R.I. scans, the telltale bright spots that marked tumor growth faded away after the treatment.

"I can't tell you what it means," Dr. Boockvar said. "Nobody knows."

Indeed, the death of the first patient was a reminder that glioblastoma can invade other parts of the brain and the spinal fluid and that the highly localized spray of Avastin might miss deadly seeds of cancer.

But Dr. Boockvar remained hopeful for the remaining patients, describing the scans as "astronomically far better than I had anticipated."

Hope and Anxiety

Mr. Sugrue was still in the hospital in late September when Dr. Boockvar burst into his room and got him out of bed to look

at his own before-and-after scans.

"He took me to this room with all these computers and said, 'I've got to show you this,'" Mr. Sugrue recalled. "This M.R.I. was a thing of beauty. I'm excited that he's excited. That means a lot to me."

Dr. Boockvar said: "Avastin may not be the best drug for this delivery technique. What's exciting about our results is that we've proven there is a local effect.

"Suppose someone said, 'I have a much better drug.' Now I can say I at least have a delivery system."

With patients, Dr. Boockvar tries to walk a fine line, trying to level with them and yet not rob them of all hope. He knows the emotional toll that a cancer diagnosis can take: his own father had leukemia for about eight years and died in September. Mrs. Sugrue said the doctor urged her and her

husband to resist doing an Internet search for glioblastoma because they would just read that it was a death sentence.

They said they tried to follow his advice, but when the subject of prognosis came up in an interview, both had tears in their eyes.

"You don't ask the question if you don't want the answer," Mrs. Sugrue said. "What will be, will be. You do what you can."

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