February 23, 2010

TARGET CANCER

After Long Fight, Drug Gives Sudden Reprieve

By AMY HARMON

For the melanoma patients who signed on to try a drug known as PLX4032, the clinical trial was a last resort. Their bodies were riddled with tumors, leaving them almost certainly just months to live.

But a few weeks after taking their first dose, nearly all of them began to recover.

Lee Reyes, 30, of Fresno, Calif., who had begun using a feeding tube because of a growth pressing against his throat, bit into a cinnamon roll.

Nothing, he told his mother, had ever tasted as good.

Rita Quigley, who had been grateful just to find herself breathing each morning since learning she had the virulent skin cancer, went shopping for new clothes with her daughters at a mall in Huntsville, Ala.

Randy Williams, 46, who drove 600 miles from his home in Jonesboro, Ark., to the M.D. Anderson Cancer Center in Houston to get the experimental drug, rolled out of bed. “Something’s working,” he thought, “because nothing’s hurting.”

It was a sweet moment, in autumn 2008, for Dr. Keith Flaherty, the University of Pennsylvania oncologist leading the drug’s first clinical trial. A new kind of cancer therapy, it was tailored to a particular genetic mutation that was driving the disease, and after six years of disappointments his faith in the promise of such a “targeted” approach finally seemed borne out. His collaborators at five other major cancer centers, melanoma clinicians who had tested dozens of potential therapies for their patients with no success, were equally elated.

In a kind of “pinch me” exercise, the six doctors sent one another “before and after” CT scans of their patients.

One was of Mark Bunting, 52, an airline pilot in Sandy, Utah. His initial scan in early October showed the cancer in his bones, an incursion considered virtually impossible to reverse. After two months on the drug, it had all but disappeared.

“Holy Cow!” Dr. Flaherty typed in reply to the slide from Dr. Antoni Ribas at the University of California, Los Angeles, that Dec. 17.

“Are you sure it is the same patient??” added Dr. Jeffrey A. Sosman at the Vanderbilt-Ingram Cancer Center in Nashville.

From New York, Dr. Paul B. Chapman of Memorial Sloan-Kettering Cancer Center, perhaps the most determined skeptic of the group, acknowledged, “This looks impressive.”

The trial of PLX4032 offers a glimpse at how doctors, patients and drug developers navigate a medical frontier as more drugs tailored to the genetic profile of a cancer are being widely tested on humans for the first time.

Throughout the fall, the only two patients on the trial whose tumors continued to grow were the ones who did not have the particular gene mutation for which the drug had been designed. They were removed from the trial. By late December, tumors in the 11 patients who did have the mutation had shrunk. Those involved in the trial held their collective breath waiting to see how long the remissions would last.

It was a far cry from where they had been a year earlier, when a previous incarnation of the drug had no effect. Urged on by Dr. Flaherty and Dr. Chapman, the companies that owned it had spent months devising a new formulation that could be absorbed at higher doses.

But the new drug, still in the earliest phase of testing, had to pass several more hurdles before federal regulators would determine whether it was safe and effective enough for widespread use.

In December, as the doctors added more patients to the Phase 1 trial, looking for the highest dose they could give without intolerable side effects, they scrambled to prepare slides with graphs and statistics to convince the Food and Drug Administration that the drug should be tested in a larger Phase 2 trial. The agency required a summary of any and all side effects — there had been only a few — and any deaths of patients on the study; thankfully, there had been none since the drug was reformulated. In a matter of days they needed to submit their findings for a prestigious meeting of clinical oncologists in June.

First, though, Dr. Flaherty, 39, needed to respond to a desperate phone message from a patient named Christopher Nelson. It came the day after Christmas.

“Dr. Flaherty,” the message said, “I need to get onto your trial.”

Hoping for a Match

The doctor had expected the call.

Mr. Nelson, 42, and his wife, Sharlene, had come to see him just before Thanksgiving. They were planning to travel to Bethesda, Md., so Mr. Nelson could enroll in a trial for a different melanoma drug. But the couple, from Jackson, N.J., had learned of Dr. Flaherty’s trial, and wanted to cover all their bases.

He liked them: Sharlene, a real estate broker who peppered him with questions, and Chris, a furniture installer around his own age with a penchant for low-stakes poker and the Grateful Dead. Both were quick to make light of a grim situation.

“I’ve gained the 60 pounds he’s lost from the cancer,” Mrs. Nelson observed. “Stress eating.”

They had met after high school, at Levitz, the furniture store where they both worked. Like Dr. Flaherty, they had two children.

“He was never sick a day in his life,” Mrs. Nelson told Dr. Flaherty. “Never had a headache, never took a sick day. I mean, can’t you give me the common cold first? It had to be cancer?”

The trial in Bethesda, run by the National Cancer Institute, involved coaxing immune cells to grow in a test tube in a procedure that worked for only a small fraction of patients, Dr. Flaherty knew.

But there would be no point in Mr. Nelson taking PLX4032 if his tumor did not carry the right mutation. For now, the doctor had a slot for only one more patient on the trial, and he and his collaborators had agreed it was almost unethical to give the drug to people without that mutation.

He wished, not for the first time, that he could snap his fingers and know the genetic profile of his patient’s

cancer cells. But getting a hospital that had operated on a patient months earlier to retrieve a tumor sample from storage could take days or weeks; the test for the gene mutation could take even longer. To speed the process, Mr. Nelson drove his tumor sample himself from Robert Wood Johnson University Hospital in New Brunswick, N.J., where it had been removed from his lymph nodes, to the laboratory at the University of Pennsylvania.

Dr. Flaherty agreed that while they waited, Mr. Nelson should proceed with the trial in Bethesda, which first required the removal of his tumor-laden spleen. Either way, that needed to go.

Mrs. Nelson thought her husband had died when she saw the stricken look on the face of the surgeon after the operation. Normally 2 pounds, the spleen had weighed 10. Mr. Nelson's liver was so enlarged that maneuvering around it had been almost impossible. And then, on Dec. 23, Mr. Nelson learned that the doctors running the trial had been unable to grow his immune cells.

On the phone, Dr. Flaherty assured him he would let them know his genetic status as soon as he found out. "If it's positive," Dr. Flaherty told him, "the spot is yours."

Checking, Checking

No one knows just what causes the single change in a single gene in a single cell that fuels a malignant melanoma.

Randy Williams, now in recovery, had gone over in his mind a million times the day he fell asleep in the sun at the lake when he was 16. His feet were so badly burned, he could not walk for a week. Twenty years later, a mole inside the arch of his left foot turned cancerous.

Was that it? Was that the moment his fate was set? Because melanoma has been linked to sunburn, especially in childhood, many of the trial's participants relived such memories. Almost certainly, each had accumulated mutations in many other genes, at other moments, over the course of their lives. Some may have inherited a gene that was already damaged.

Once unleashed, however, any cancer seemed to rely on the protein made by a particular mutated gene to fuel its wild growth. In all of the PLX patients, that gene was B-RAF. And whatever the cause, they came to consider themselves, so far as it was possible with what has always been a virtually untreatable cancer, charmed.

At least they had a chance. The patients took pills the size of large vitamins, twice a day. Some gulped them down with water. Others spooned them up with applesauce.

To get to the mandatory doctor's appointments where patients were given precisely one month's supply, Mr. Williams, a contractor with two teenage children, drove all night with his brother in a pickup truck. One young woman hopped "corporate angel" flights on private jets whose owners donated empty seats.

Mark Bunting used his pilot privileges to commute to Los Angeles to see his oncologist. "He says," Mr. Bunting told friends as his tumors melted away last fall, "that I'm the leader of the pack."

For some patients and their family members, though, the sudden reprieve was almost as disorienting as the diagnosis.

Mr. Bunting, for one, could not convince his wife, Trish, that it was for real.

A former flight attendant, she had coped with her husband's cancer by confronting it head-on. She organized a family trip to Disney World, so their young children would have the memory. She entered nursing school, so she

would have a means of supporting herself.

As if to drive home the point, on her first day, a teacher had illustrated a lesson on cell growth with a picture of melanoma that had metastasized. “Here’s when I think of one of my favorite Carole King songs: ‘It’s Too Late,’ ” the teacher said.

Now, even as Ms. Bunting watched the color seep back into her husband’s gray skin, even as they celebrated a Christmas she never thought he would live to see, she found herself unable to shake the need to prepare for his death. “You need to sit and write down stuff for me,” she told her husband. “I need to know who I call for this, I need to know where things are.”

“But I’m doing better!” he pleaded. “Can’t you see?”

In Oklahoma City, Kerri Adams, 30, just tried not to jinx it. She did not look up anything about the drug, the gene or the cancer on the Internet or anywhere else. Single and employed as an analyst at a local utility company, she attended church with her mother and ate dinner with friends. But when they coaxed her to meet new people, she demurred. The future seemed too uncertain.

Mr. Williams, back full time at his contracting business with his brother, climbed ladders, lifted weights and fixed up his Corvette.

The tumors on his legs that had constantly oozed blood dried up and then disappeared. Yet every day, he ran his fingers over the spots where they used to be, checking, checking, checking.

“I don’t think I’ll ever believe,” he said, “that it’s not coming back.”

A Doctor’s Struggle

Still waiting to hear if he would be eligible for Dr. Flaherty’s trial, Mr. Nelson managed to get to a Portuguese restaurant with the rest of the family for his son’s 16th birthday in January 2009, but he could not eat.

One morning a few weeks later, the pain in his stomach was so overwhelming that he told his wife they needed to go to the emergency room, where he was admitted and hooked up to intravenous morphine for the pain.

“There’s nothing we can do for him,” the doctor told her. “You should think about getting hospice.”

Frantically, Mrs. Nelson left a message for Dr. Flaherty. She wanted to order an ambulance, an airlift, whatever it took to get her husband to Philadelphia.

He called back immediately. The test had finally come back, he said.

Mr. Nelson had the mutation.

“Is my husband going to be able to get on this drug?” she demanded. “I need to know because there’s no waiting.”

First, she would need to wean him from the auto-drip morphine, Dr. Flaherty told her gently. To qualify for the trial, he needed to be able to walk in. And the last spot on the trial had to be filled within a week.

Mr. Nelson, who had not eaten in days, threw up the morphine pills the first several times he tried to get them down. But he went home the day before Valentine’s Day.

“Honey,” his wife told him, “you don’t have to get me anything.”

At home, Mr. Nelson called her on her cellphone as she waited in a long pharmacy line to pick up the morphine. The pain was breaking through.

“Hurry,” he said.

Mrs. Nelson drove to Philadelphia a few days later, her husband sprawled in the back seat. At the cancer center, she pushed him in a wheelchair into the waiting room of the melanoma clinic. When the nurse called his name, he struggled to his feet and walked in to see the doctor.

Dr. Flaherty looked at him. He did not need the required blood test to tell that his numbers were off the charts. Mr. Nelson’s eyes were yellow, a sign that his liver was at the edge of failure. He had, at the most, the doctor thought, a month to live.

Maryann Redlinger, the clinical trial nurse, was not one to mince words.

“Are you out of your mind?” she asked Dr. Flaherty when he told her he wanted to put Mr. Nelson on the trial. A death on a trial was a black mark. No matter how good the other numbers were, it would count against them.

If his decision delayed by even a few months the approval of a drug that could help tens of thousands of patients, surely it would be unethical. But there might be a benefit in seeing what the drug could do for a patient like Mr. Nelson. This was the kind of patient who came to him all the time.

And how could he deny Chris Nelson a drug that, he knew in his gut, would give him extra time?

“He has two kids at home, Maryann,” he said. “Do you want to tell him he can’t get it? Go ahead, you call him up and tell him no.”

Dialing Back

The side effects struck at the 1,120-milligram dose.

Many patients had been taking the reformulated drug for five months with no signs of relapsing. The doctors had hoped that by pushing up the dose they could shut down the cancer more effectively. Some patients were taking as many as 28 pills a day.

Ms. Adams, in Oklahoma City, woke up one morning covered in a rash. Frightened that she would be dropped from the trial, she tried to ignore it. But at work, her boss was horrified and insisted that she call the doctor. Another woman’s hand swelled up, and she could not make a fist. A Philadelphia patient had horrible nausea and diarrhea, and Mr. Bunting’s joints grew so stiff that he had to hand jars to his wife to remove the lids, even when they had already been opened.

Maybe the drug, designed to turn off only the defective B-RAF protein, was, at high doses, also affecting its role in healthy cells. Or perhaps it was interfering with other proteins the body needed to function properly. On their next conference call, the doctors agreed that they had to dial back the dose.

As the side effects began to subside, many of the patients began to believe they had beaten their cancer. One evening, Mr. Bunting performed what had become his pill-taking ritual as his wife puttered around the kitchen.

He liked the water to be room temperature, so he heated it in the microwave and added cold from the tap. He burped, and some powder from the pills came out of his mouth just as she turned to look.

They both laughed.

One Step Forward ...

When Mr. Nelson strolled into the University of Pennsylvania for a scheduled day of blood work and monitoring in mid-March, Ms. Redlinger greeted him as if he had risen from the dead.

Gazing out the window of the clinic room, he spied a hot dog stand.

“Dirty water dogs,” he exclaimed.

“Can you get me one?” he asked his wife’s sister. “Actually, two?”

“Chris is feeling better,” the nurse told Dr. Flaherty casually when she saw him.

“What do you mean?” he pressed.

“Well, he’s off pain meds,” she said.

Dr. Flaherty was not scheduled to see Mr. Nelson until three weeks later. But between appointments that day, the doctor found time to visit his patient. In Mr. Nelson’s room, he broke into a wide smile, a tension he had not realized he was holding seeping out of him.

He had never seen a melanoma patient who had been that sick improve that much. He was not sure he had ever seen a melanoma patient that sick who improved at all.

Mrs. Nelson hugged him. In the weeks that followed, Mr. Nelson gained 17 pounds. One morning a friend drove him to Atlantic City, where for a $35 buy-in, they played his favorite game, Texas hold ’em, all day. The drug had made him sensitive to the sun, and he burned his skin cleaning the pool one afternoon, even with strong sunblock. Mrs. Nelson bought an umbrella, and he spent much of the spring sitting underneath it.

“Today’s a nice day,” he said over the phone to a friend in early May. “There’s a cloud, and the sun is behind it.”

In mid-May, right before he was to fly to Orlando, Fla., to present the trial’s data, Dr. Flaherty received a message on his BlackBerry as he was walking on campus.

The first patient to respond in the trial, Elmer Bucksbaum, had been admitted to the hospital. The cancer had spread to his brain.

Dr. Flaherty stopped walking.

The drug, Dr. Flaherty knew, was powerless in the brain. But had the drug held off the cancer elsewhere in Mr. Bucksbaum’s body? Or would other patients, too, begin to relapse?

Mr. Bucksbaum died a few days later.

Dr. Flaherty called his family and offered his condolences. It had been not quite eight months.

Wednesday: The Next Hurdle.