

Immunotherapy Offers Hope to a Cancer Patient, but No Certainty

Drawing on his immune system to fight Hodgkin's lymphoma, my friend saw a stunning improvement. Then came the relapses.

By MATT RICHTEL JULY 31, 2016

DENVER — A cancer patient nicknamed the Steel Bull got his death sentence on a gloomy March Wednesday in 2015.

He was 47, his given name Jason Greenstein, but he had earned the moniker from his oncologist for his stubborn will during more than four years of brutal chemotherapy and radiation treatment — all of which had failed.

That Wednesday, March 4, his left side bulged with 15 pounds of tumor, doubling in size every few weeks. Lumps of Hodgkin's lymphoma cells swelled in his lungs, making it hard to breathe, impinging a nerve and nearly paralyzing his left hand. Yet Mr. Greenstein, ever the optimist, was not prepared for his doctor's frank words when he displayed his latest symptom: tumors along his right jawline, the first spread of cancer to that side.

The oncologist, Dr. Mark Brunvand, said he excused himself to the hallway to gather his emotions. When he returned a moment later, he looked Mr. Greenstein in the eye.

“You are going to die,” he remembers saying. “And because you’re my friend, it’s my job to make you as comfortable as possible.” Behind the doctor stood Mr. Greenstein’s case manager, Poppy Beethe, crying.

In a note to himself afterward, Dr. Brunvand described further treatment as “more toxic than beneficial,” and unwarranted “unless he has dramatic response.”

What happened next qualified as well beyond “dramatic response.” A few days later, Mr. Greenstein agreed to try a last-ditch drug called nivolumab that was being tested for Hodgkin’s. It dripped into his veins, just like those body-racking chemotherapy treatments. But this time, there were no harsh side effects. And this time, the outcome was very different.

Three mornings later, Mr. Greenstein woke up to shock from his girlfriend.

“Jason, you’ve got to see this!” she said. She looked at his back, where the cancer had so bulged that she affectionately called him Quasimodo. “Your tumors have shrunk!”

In an eye blink, after years of agonizing and futile treatment, Mr. Greenstein’s cancer would disappear. Within weeks after that first treatment, his doctors declared him in remission.

It was a result that put him at the vanguard of a new generation of cancer treatment called immunotherapy that casts into sharp relief the harshness of how we have long treated cancer and the less grueling way we might. Immunotherapy’s aim is to prompt the immune system, which is often stymied by cancer, to attack tumors with the zeal and sophistication that it attacks other diseases. The concept, at least in a primitive form, stretches back more than a century, but only in recent years have therapies been developed that show its true promise — and, for now, its limitations.

In that astonishing span of six weeks, few of immunotherapy’s successes seemed as dramatic as Mr. Greenstein’s. “His story is not just one in a million,” Dr. Brunvand marveled, but “one in 20 million.”

On a personal level, this stunning medical reversal was not entirely surprising to Mr. Greenstein's family and friends. Jason and I were in a tight circle of high school buddies in Boulder, Colo. To us, he has always been a fierce competitor who attacked the world with passion, humor and unbridled optimism — along with, at times, inattention to detail and procrastination. Life was always an adventure, including Jason's death match against cancer, which he allowed me to chronicle.

Then again, cancer is not easily beaten. And for all its promise, immunotherapy for now brings more disappointment than marvel for the majority of patients. The end of this story, sadly, allows no easy ebullience. Not for medicine. Not for Jason.

In the Shadow of Cancer

When the symptoms hit in 2010, Jason was living in Las Vegas, where he had started a company called Green Man Group. It sold trinket boxes to casinos for use as gifts.

Jason went to both law and business school and was obsessively entrepreneurial. He loved selling and schmoozing with customers on a noon-to-midnight instead of 9-to-5 clock. Visiting casinos, he crisscrossed the country in an aging Chrysler Concorde, often with Skoal tobacco packed in his lip. He had come from tobacco users; his dad had smoked cigars, his mom cigarettes since age 14.

It was unseasonably warm on May 10 when Jason, driving back to Las Vegas from Arizona, felt his throat tickle and his head hurt. His legs had felt heavy for several months. Several days later, he attacked the symptoms with a homegrown remedy: He downed most of a 12-pack of Bud Light Chelada.

"It didn't work out too well," he said with a laugh, looking back. He felt worse in the morning.

My first memories of Jason come from the dugout. We were teammates for years in Little League. I was a two-bit player and Jason a perennial All-Star —

center fielder and shortstop, leadoff hitter. He had the same gifts in football and basketball. Not just that — he was funny, self-effacing, a good student and a good guy. His junior high nickname was Golden.

But all was not golden for Jason. One morning in eighth grade, our friend Tom Meier found him in the locker room, sobbing. Jason had learned the day before that his dad, Joel, at 46, had been told he had colon cancer.

“Here was the strongest person I knew, and he was absolutely shattered,” Tom said.

Over the years, Jason’s friends and family would debate the extent to which his father’s cancer and eventual death, in the summer before our senior year of high school, unmoored Jason. He had been Jason’s first coach and chief advocate, attending every game, often chomping a stogie, stoic and hunch-shouldered. In the weeks before he died, he watched Jason, a 5-foot-9 point guard, help lead Boulder High School to a state basketball championship game.

After his father’s death, Jason’s senior-year grades tanked such that he had to explain them to Occidental College, where he was to play basketball and baseball. A manic side of Jason became more prominent. He never settled down with a family, and his businesses came and went. His inimitable passion remained, while his follow-through sometimes faltered.

“Dad was his guru; I don’t know how to describe it,” Guy Greenstein, Jason’s older brother, and one of five siblings, told me. “When my dad was gone, he was left to flounder a bit.”

After Jason first felt sick, one doctor diagnosed mononucleosis, but two courses of antibiotics did not work. Each week, he felt more rundown, until one day in August, he could not get off the couch. “It reminded me of my dad,” Jason reflected. “He had never done that before, and then he started lying on the couch.”

At summer’s end, a family doctor told him he had Hodgkin’s. It was the best case of a bad-case scenario — Hodgkin’s has a 95 percent cure rate.

No problem, Jason thought, I'll get it cured and move on.

Beaten Down by Treatment

In 1990, Dr. Brunvand, was climbing Mount McKinley when he and his group got a distress call from 19,600 feet. Seven Japanese climbers needed rescue in 100-mile-an-hour winds. Dr. Brunvand, then huddled at 17,000 feet, helped bring six of the climbers back alive. His tenacity made him a perfect match for Jason, and he knew what he would be putting Jason through.

Dr. Brunvand, 60, a bow-tie-wearing veteran in his field, likens traditional chemotherapy to napalm. It kills not just cancer but other rapidly dividing cells, like the ones in the gut, hair follicles and mouth. "When you have cancer, you spread napalm on it and burn everything to the ground."

Jason received his first treatment in September 2010 in Denver. A thin nurse with a kind smile hooked him to an IV. He tried to read, and felt like he did not belong with the line of sick people in chemo chairs. Into his veins dripped a four-drug cocktail called A.B.V.D. that has been in wide use since the 1980s.

After chemo, he described feeling "the sickest you've ever felt but multiplied by 10."

In spring 2011, after a brief remission, Jason became one of the unlucky few with Hodgkin's; his cancer recurred in his chest wall. He moved to the next level of treatment, "salvage" chemotherapy with the acronym ICE. Side effects: diarrhea, bruising, bleeding, hair loss, sore mouth.

That winter, he got a round of high-dose chemotherapy followed by a stem-cell transplant. Before the transplant, he met a psychologist at the Colorado Blood Cancer Institute, and, to prove his zest for life, Jason played air guitar and sang to her, wearing sunglasses.

But when the psychologist, Andrea Maikovich-Fong, went to see him in the hospital after his transplant, he was slumped in a hoodie. "He looked like this

shadow sitting there. He looked up with his eyes, and not his chin, and said: “This is terrible,” she recalled.

This was what I, and others, began to see. Cancer had not beaten Jason yet; treatment was starting to. When we talked by phone, he sometimes wept about his pain, exhaustion, pill regimen — 15 medications or more daily, an alphabet soup of drugs, from acyclovir to fight infection to Zofran for nausea.

Once, he showed up at the hospital after an all-night drive from Las Vegas with his red blood cell count so depleted (20 percent of normal) it could have killed him en route. He crawled to the elevator, where he was discovered, and then, while being wheeled away, joked with Dr. Brunvand that he had been in Las Vegas spending money on “hookers and blow.”

“It’s hard not to love a guy who sees God with one eye and the seedy side with the other,” Dr. Brunvand said.

In fall 2013, Jason was in remission again, finally, he said, feeling like himself. Then, the morning after his beloved Denver Broncos were crushed in the 2014 Super Bowl by the Seattle Seahawks, Jason’s phone rang. It was Ms. Beethe, his case manager. “Jason, I have some bad news.” Another relapse, tests showed.

“I didn’t know what was worse,” Jason grimly joked later, “getting cancer again, or the Broncos losing. Any true Bronco fan would say it’s a tie.”

Jason came up with an analogy to describe being a patient in a fight with cancer; in his analogy, healthy people live in a village on a beautiful Tahitian island while cancer patients float around it in canoes.

“The doctors pull on the rope and pull me back to the pier. I can still visit the people in the village. But I’m drifting further and further,” Jason said. “All around me are coffins — the people who died from cancer. I’m waiting for my canoe to turn into a coffin.”

A few weeks after the Super Bowl, his friends planned a weekend for him in

Boulder to, without putting so fine a point on it, say goodbye. Tom came from Minnesota and I from San Francisco. Jason, true to form, showed up to his own party two hours later than everyone else, having made a marathon drive from Las Vegas. At the end, we all said goodbye in the parking lot. I assumed I'd never see Jason again.

Crossing a Threshold

Jason battled for another year, until March 2015, when he received his death sentence and his family met with Dr. Brunvand to plan hospice care. Without much hope, they agreed to take a flier on a drug called nivolumab, part of the new frontier of immunotherapy.

Nivolumab had been approved for advanced melanoma in 2014. An article published that year in The New England Journal of Medicine reported the drug's remarkable effect on relapsed Hodgkin's patients, albeit in just 23 people. Dr. Brunvand's team managed to get a dose, though it was not yet on the market for Hodgkin's, through a program called "compassionate use."

Dr. Brunvand expected little. The evidence was scant, Jason so far gone.

"When I start to pray, I know it's time to let go," Dr. Brunvand said. "I'd started to pray for Jason."

Immunotherapy is based on the fact that once the immune system recognizes cancer and gears up to fight it, something remarkable happens: The immune system is rendered helpless.

Scientists believe that the cancer sends signals to put the brakes on our T-cells, which are the ones that fight disease. A crucial way the tumor tricks T-cells is by displaying on its surface a protein that is recognized by the T-cell through a receptor called PD-1. It stands for "programmed death." It tells the T-cell to, in effect, self-destruct.

This might seem like a serious design flaw. After all, why would immune cells

commit suicide? It turns out that the PD system is essential to survival: It is fail-safe against the immune system attacking our own bodies (see: lupus, Crohn's disease, rheumatoid arthritis). Sometimes we want our bodies to halt the system; cancer takes advantage of this survival mechanism.

As Jason slogged through chemo, researchers around the country were experimenting with developing a so-called PD-1 inhibitor for cancer so as to unleash the immune system. This concept was at the heart of the nivolumab treatment that Jason was about to receive.

On March 13, Jason's girlfriend, Beth Schwartz, drove him to his first treatment. On the ride, he was not thinking about surviving, but about having his pain managed well enough to see his nephew Jack play that night in the state high school basketball tournament.

Mid-afternoon, Jason sat in a recliner in the bleak, boxy room. A nurse in a blue gown cleaned his central line, an intravenous port in Jason's chest. She gave him steroids. Jason couldn't move his left arm or close his hand, the nerve so squeezed by Hodgkin's.

She hung a translucent bag from an IV pole. It held saline and 200 milligrams of nivolumab. The treatment lasted an hour. At least there were no side effects; this was not scorched earth but immune-system tinkering. Then Jason went to his nephew's game and sat with a former high school teammate, Dan Gallagher, who thought: "He looks so bad, I wonder if he'll make it through the night. It was like looking at his dad again."

Three mornings later, when Beth exclaimed that Jason's tumor had shrunk, she wondered if she might be imagining things. So she decided to take pictures each day of his back.

The evidence startles. On Day 1, his left half still looks like the Incredible Hulk, a veritable watermelon protruding. If you squint, you can see it shrinking by Day 3. Then, at two weeks, he looks slender, normal definition having returned. He had more nivolumab. Then he went for a follow-up appointment.

What happened to my cancer, he asked Dr. Brunvand, using an expletive.

“I watched the moon landing in 1969, and it was a similar sense of awe,” Dr. Brunvand said. “It was that same sense we’d crossed a threshold,” he said, adding, “I’d just seen the power of the immune system.”

This is when I started taking notes. How could this be possible? Was this, indeed, a miracle?

I spoke to Dr. John Timmerman, an oncologist at the University of California, Los Angeles, who was among the researchers on the paper in The New England Journal of Medicine. I told him Jason’s story, and he said, “Wow.”

But he also said, “I have seen some pretty remarkable cases similar to this.”

In 2013, Dr. Timmerman treated a 27-year-old woman “near death’s door,” in such pain she could hardly move or sit down. She took the drug. The results: “A miracle,” he said. “The next time she came in, two weeks later, she popped up on the exam table on her butt and my jaw dropped.”

In almost the same breath, Dr. Timmerman offered a warning. “We’re in the honeymoon period,” he said, and for one crucial reason: “Patients are responding. They are also relapsing.”

Sometimes, tumors return in a few months or a year, sometimes not.

“I stay awake at night trying to get us beyond the honeymoon,” Dr. Timmerman said. “How do we leverage this into a cure?”

Dr. Brunvand, who had worked in his first AIDS clinic in 1986, hopes immunotherapy leads to fruitful, pain-free lives for cancer sufferers just as antiretroviral drugs have for people with H.I.V. In summing up his hopes for immunotherapy in cancer, he says, simply, “Think Magic Johnson.”

If Dr. Brunvand is right, some future Jason might not only survive but also not be driven to the edge by the treatment itself. For now, though, life on medicine’s

cutting edge is no bowl of cherries, not with your survival at stake. Jason relapsed in August 2015.

Independence Day

On Aug. 13, a resplendent Colorado day, Jason pulled up to my in-laws' house in Denver, where I was visiting. He was a broken man. He moved slowly, hunched at his shoulders, wore Ray-Bans and looked to me like a character in "Dallas Buyer's Club."

We sat in the backyard. Jason sobbed.

"No matter how many times they tell you you've got cancer, you don't get used to it," he said.

He mourned the toll it had taken on his family, especially on his mother, who supported him emotionally and financially.

"I think it would be easier for everyone if I was dead."

He asked for ice for his dry lips.

But would you believe it? Jason wasn't done.

He went in for radiation treatment, and soon appeared to have beaten the cancer back again.

"It's awesome. I'm so psyched, dude," he told me on Oct. 5. He was thinking of new business ventures, including working with a cancer doctor and researcher to develop an immunotherapy company. "I'm living proof!"

In early April this year, I called him to check in. Jason did not pick up or call back. After several days, I called Dr. Brunvand.

"Jason's relapsed," he said. "Ten days ago."

He had been shoveling snow at his mother's house when he felt his back go

out. In excruciating pain, he went for an M.R.I. and other tests. They found evidence of Hodgkin's in a vertebrae in the middle of his back and in the lining of his spinal column. Soon, his seventh vertebrae fully collapsed, an agonizing compression fracture, due in part to years of bone-density-depleting therapies.

"The treatment is killing him," his mother, Catherine, told me when I arrived to visit on April 19. Jason sat in a recliner in the living room, in such agony he could hardly move. Heavy pain medications made him delirious.

The next day, it took three nurses to gently lower him into a wheelchair outside the hospital, where he got a course of immunotherapy to treat Hodgkin's in his spinal column.

On May 17, the Food and Drug Administration approved nivolumab for patients with Hodgkin's lymphoma in cases like Jason's, where the patient has relapsed or the cancer has progressed after a transplant.

Jason got his last dose of the drug in late May. On June 1, he got the results of his latest scan. The tests showed no trace of cancer. But he was still in the hospital, virtually immobile, recuperating from surgery to stabilize his back with rods, and facing complications from coming off pain medications and steroids.

On June 21, I woke to a text from Dr. Brunvand. "Jason has taken a dramatic turn for the worse."

Jason, who had been in the hospital for more than 70 days rehabilitating from the surgery, had suddenly stopped talking, his eyes closed most of the time, glassy and not home when open. Flummoxed, Dr. Brunvand could not find anything on brain or blood scans, ultimately deciding it was encephalopathy, meaning his brain had temporarily shut down to flush out toxins.

Too many drugs for too many years. Specifically, Dr. Brunvand reasoned, the awakening of his immune system had led to inflammation in the nervous system.

Jason was moved to intensive care, where he had a feeding tube, catheter,

intubation. Dr. Brunvand ordered a spinal tap to give him steroids to combat the inflammation. But frankly, we all braced ourselves.

“I think he’s lost the fight in him — and why wouldn’t he?” his mom told me.

I sent a text for his sister to read to him: “Richtels send their love.”

Over the next few days, Jason remained enveloped, struggling not to be pulled under by toxins, as he had been doing for years against cancer. On July 4, his girlfriend was sitting by his side in the intensive care unit when his eyes popped open.

“He’s awake!” she texted me. Happy Independence Day. He voraciously ate soup and applesauce. He watched the Colorado Rockies game. After a few days, the doctors told him his back was healing and they expected to send him home within weeks.

On July 7, Jason texted a response to the note I’d sent while he was in the I.C.U.

“Thanks,” he wrote. “Better and trying for a comeback.”

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