# ‘How do you decide?’: Cancer treatment’s CAR-T crisis has patients dying on a wait list

By Angus Chen

Within two years of being diagnosed with multiple myeloma, Shawn Goltzene had blasted through nearly all his options. An initial stem cell transplant couldn’t hold off the cancer for more than half a year. With each new therapy his doctors tried, the cancer would surge out of remission within weeks — striking the bones in his back and legs.

“We hit him with everything, the whole kitchen sink,” said Krina Patel, the director of the myeloma cell therapy program at MD Anderson Cancer Center and Goltzene’s clinician. She tried putting him on a clinical trial for an immunotherapy drug. “It blew right through him. He quickly got to fourth-line therapy.”

By the fall of 2021, Patel saw only one possibility left to save Goltzene’s life — a newly approved CAR-T cell therapy for myeloma. In clinical trials, this type of personalized immunotherapy had shown remarkable efficacy in patients with stubborn myeloma, offering them months or years of healthy life that they would never have otherwise experienced. Goltzene was about to become eligible to receive it, but Patel had to warn him that being eligible wasn’t enough. They would have to make their case for something all too rare: a cell-manufacturing slot.

It’s an approach that is transforming treatment of blood cancers: CAR-T therapy labs convert the immune system’s T cells into assassins of cancer cells by inserting a gene for

what's known as a chimeric antigen receptor. But the process is slow and laborious, and drugmakers simply can't keep up.

The shortage of CAR-T therapy for multiple myeloma is creating a gut-wrenching dilemma for clinicians — one that they must debate each week at CAR-T myeloma programs like Yi Lin's at the Mayo Clinic. She's the medical director for Mayo's cellular therapy program, and Lin explained that doctors must decide which of their dozens of eligible patients will get one of a few coveted CAR-T spots each month. That means they also have to decide which ones will need to wait longer, giving their disease time to attack. For patients, that might mean becoming too sick to benefit from CAR-T in the future, and losing their shot at the therapy.

Patients like Goltzene often end up stuck on a waiting list for months. "And people are dying — about 20% of all our patients together are actually dying before they can get CAR-T," Patel said, a figure that myeloma doctors at Mayo and Dana-Farber Cancer Institute said reflected their experiences as well.

These waiting lists are expanding. Patel estimated her center gets about 10 new patients each month who are eligible for CAR-T, but they're able to give the potentially life-saving treatment to only five patients each month. That's just at MD Anderson, one of the country's largest and most prestigious cancer centers, Lin pointed out. Many of the roughly 70 cancer centers that can prescribe CAR-T get less.

"The median is 1 to 2 slots per month," Lin said. "It ranges from 0 to 4 per center, and some cancer centers get no slots." As a clinician, she said, "you have to pick off a list of close to 100 patients to get these slots." While representatives from Novartis, Bristol Myers Squibb, and Janssen, all of which produce CAR-T products, told STAT they believed the industry was rapidly expanding its capacity to create CAR-T cells, others across pharma and health care said the problem was getting worse. The shortage in CAR-T is currently a crisis for just myeloma products, but experts said supply chain constraints in some of the raw materials needed to create CAR-T cells may spill over to lymphoma and leukemia treatments — especially as the therapy becomes eligible to more patients as a second-line therapy.

Clinicians are already noticing longer manufacturing times for CAR-T cells, including myeloma and lymphoma products, Lin said. That makes it even harder to decide which patients might be able to wait long enough to get a CAR-T slot and survive the weeks-long manufacturing process.

"That's the hardest part," Lin said. "How do you pick the patient that you think their disease is not going to progress quickly enough that they get too sick to get the treatment

and are still healthy enough in the next few months to get to the CAR-T dosing? How do you decide?"

It wasn't clear if Shawn Goltzene would live long enough to get CAR-T therapy. An accountant, he discovered he had cancer two years ago. His bones would throb as he jumped up and down while working out at his gym, so he started seeing a chiropractor to help relieve some of the pain. But on the last visit, the chiropractor snapped one of Goltzene's vertebrae. The myeloma had weakened his spine so much, it couldn't take the stress of popping joints.
"I was in the ER and I found out, No. 1, that I had a broken back and, No. 2, I had cancer," Goltzene said. "The break on T12 has never recovered. He damaged it pretty bad."

Everything changed. Goltzene had been an avid hiker, camper, and traveler before myeloma struck. Throughout his 30s and 40s, before he married and became a father, he traveled to over 40 countries. "I'm on my fourth passport," he said. "I filled out all the pages on the other ones." But the cancer and the fracture in his spine cut into his mobility. As his disease progressed, the myeloma would repeatedly hit the spot of the break. He became barely able to walk up steeper inclines.

"Going up and down terrain, I just didn't get there. I can't do that without being in a lot of pain. And the fatigue can be really frustrating," he said. "With the myeloma, all the physical stuff came to a screeching halt."

When he first got diagnosed, Goltzene lived in Ohio, and a local oncology team gave him a stem cell transplant. The oncologists wanted to follow up with a second transplant, but Goltzene had reservations. He got in touch with Patel from MD Anderson and felt she was a better fit for him. So, last July, Goltzene moved himself, his wife Phuong, and his three kids from Dayton to Houston.

"Dr. Patel agreed there were so many other options on the table, so I decided, you know, to pack everything and move us down to the best doctors possible," Goltzene said. "It was whatever we can do to slow down or beat this cancer."

But within a few months of being in Houston, Goltzene had already barreled through practically all of his treatment options. “He got a complete response to his initial transplant, but Shawn had ultra-high-risk disease,” Patel explained. “The myeloma came back slowly. We put him on a three-drug maintenance, and it lasted a month before he went into full relapse. I put him on all the standard of care treatments left, sort of our biggest guns. It worked for a month.”

CAR-T therapy currently can only be given to patients as a fifth-line therapy, and Goltzene was approaching his fourth. But the earliest available CAR-T slot probably wouldn’t be until February 2022, four months away.

Every week, myeloma doctors like Patel meet to decide which myeloma patients at their hospital will get a CAR-T slot — and which ones won’t. Clinicians debate each case, trying to balance between advocating for their sickest patients and those who might be most likely to benefit. There are no national guidelines to help doctors make their recommendations.

“It’s a terrible problem to have,” said Mayo Clinic’s Yi Lin. “I surveyed 17 centers across the U.S. They’re all trying to figure out the best, ethical way to give CAR-T. Some of the qualitative responses — it’s gut-wrenching to have patients who die on the waiting list, who go to hospice on the waiting list, because they just ran out of time and options.”

Because every CAR-T cell dose is made from the patient’s own cells, they must be manufactured individually at specialized labs. Drugmakers only have enough capacity or raw materials to provide each cancer center with a limited number of manufacturing slots each month. If something happens to the patient while their CAR-T cells are being made, that slot’s used up — and the cells may be wasted.

That’s an experience Lin knows too well. In the early days when the first myeloma CAR-T from Bristol Myers Squibb, ide-cel, had just been approved, Lin and her team picked the sickest patients. One of them, she said, was just healthy enough to have his T cells collected for the drug.

"Within days, after collection, the patient got really weak, tired, didn't look right. The disease just took off. We did everything to keep this patient's disease under control — and he died before he could get the CAR-T," Lin said. "That one hit us really hard. We didn't think he would progress that rapidly. It felt like we failed that patient, and maybe that slot would have helped another. It's heartbreaking."

Those experiences are forcing clinicians to think harder about which patients should get slots. Now, Lin said, each myeloma physician advocates for the patients under their service, and the group examines each individual case. They need to make sure that every patient who they move forward with CAR-T is going to benefit, Lin said, because one patient getting it inevitably means another person won't.

"We try to maximize total benefit now," she said. That means figuring out which patients are most likely to survive the long wait time to receive their CAR-T therapy. "What treatments has the patient had before? What other drugs might be left for them? What has been the trajectory of their myeloma disease?"

But predicting which patients will remain healthy enough to wait months for a CAR-T slot and which ones won't can be difficult with myeloma, Lin added. Patients who appear to be doing well can deteriorate rapidly. Others, with terrible disease, can hang on long enough to receive cells and experience a remarkable turnaround.

"I have one patient where I've been trying to manage for years, and she never qualified for trials because she had such bad myeloma," Lin said. "I took her through transplant, really harsh chemo, with the hope that I can just keep her alive until CAR-T approval."

After ide-cel's approval in 2021, Lin said there was a small window where her patient was healthy enough to get CAR-T. "She did amazing. I was so worried about her disease. We were bracing for side effects, but she sailed through and remains in remission today," Lin said. "I've had a patient tell me this is the best day they've felt — that they remember how they feel before myeloma. It's not trivial."

When Patel brought up Goltzene's case to the myeloma committee at MD Anderson, she acknowledged that she couldn't be sure that "his disease would be able to behave long enough to get CAR-T." Infections, low white blood cell counts, and other complications can make CAR-T too dangerous to attempt. She told the team about the clinical trial for a drug called a bispecific antibody that Goltzene had to drop out of. Myeloma began growing in his pelvis and spine again, forcing Patel to give him emergency radiation and chemotherapy in the hospital.

That would have to last him until a CAR-T slot opened up. Patel and the rest of the myeloma team agreed he should get a shot at the therapy. “For Shawn, this was his only chance,” she said. He had no other options. They put him near the top of the list. It didn’t hurt that he was only 51 and had three young kids at home.

At the end of January 2022, Krina called Goltzene to let him know a CAR-T slot had opened up. The radiation and chemo had calmed Goltzene’s myeloma down long enough to collect cells, and she wanted to do so as quickly as possible. “We were able to get you a slot,” she recalled telling him. “This is fantastic, but it means there’s a lot we have to do.”

As Goltzene listened to Patel explain the steps he would have to do in the coming days, a wave of relief massaged his body. He and his wife popped open a bottle of champagne that night. “A small celebration,” he said.

But Patel remembered being wracked with anxiety. Of all her patients, Goltzene needed the CAR-T the most, and she was happy to finally be able to offer it to him. At the same time, managing Goltzene’s myeloma was like battling a dragon, and she was terrified because it would still be weeks until Goltzene could receive his CAR-T cells. During that time, anything could happen.

“It was scary because he blew through the bispecific, and we don’t know why he didn’t respond,” Patel said. “I was really excited to tell him he got it, but I was scared. Was he even going to make it through to get the CAR-T?”

The stretch between T cell collection – or leukapheresis – and infusion of the CAR-T cells into the patient is known in the industry as vein-to-vein time. If all goes well, it could take about three weeks with current technology, but the actual wait time is often longer. Getting the patient evaluated and ready for CAR-T and to have the cells collected in the first place might take several days, Patel said. Doctors need to separate the T cells from the blood and then ship them to the manufacturing facility.

There, technicians need a couple of days to prep the T cells and genetically engineer them using the viral vector to give them the CAR. This synthetic protein is the tool CAR-T

cells use to recognize and destroy cells that may be cancerous. Next, the manufacturers must grow enough of the new CAR-T cells to dose the patient, which may take several more days. Then, there's a 7-day sterility test and quality assurance that ensures the product is pure, clean, and ready to give to patients. The finished CAR-T cells are frozen and shipped back to the hospital. Usually, patients must then go through an additional five days to do chemo and rest before the doctors and nurses thaw the CAR-T cells and infuse them into the patient.

In reality, this entire process often runs slower than about three weeks. Things can go wrong at any step of the way for a variety of reasons, including the fact that patients' cells can arrive in an unhealthy state. "CAR-T usually takes about four to five weeks door to door in the best-case scenario," Mayo Clinic's Lin said.

But one major problem is that the drug manufacturing process is antiquated in many facilities, said Kwok Pang, an executive at the cell and gene therapy biotech Autolomous. "To manufacture a medicine, there's a number of things you must do," he said. "One is to capture manufacturing data appropriately as it goes through different groups of individuals — the operations team, the quality teams, the clinical teams."

All of that is required to make sure the product is being made safely. Many drugs can be made in large batches, requiring only one set of documentation for millions of doses, but CAR-T can only be made in batches of one. "Because it's made from the patient's own cells, right?" Pang said. "And it's an entirely manual process. They're actually using pen and paper to capture all their manufacturing data."

Many of the manufacturing steps are processed by hand in many facilities, too. That introduces a higher potential for error compared to digital systems, Pang said. If the record keeping can be made entirely electronic and easily shared across all the stakeholders in the manufacturing process, like the hospital, the shippers, and the drugmakers, Pang said CAR-T cells could be made 40% faster. With the platform that his company is building, "Possibly even more," he said.

Pharmaceutical companies are working to improve the vein-to-vein time by automating some processes and testing new technologies. Kite, Novartis, and Bristol-Myers Squibb have also built digital platforms for CAR-T. Those systems are now being integrated into new and existing facilities, said Lynelle Hoch, the global cell therapy franchise lead at Bristol Myers Squibb.

Still, right now, myeloma clinicians told STAT the average vein-to-vein time is about five to eight weeks for CAR-T cells. That's just about how long Shawn Goltzene had to wait for his cells, too.

It started out well, Patel said. Goltzene's care team was able to collect his T cells the second week of February this year. He was doing well at the time, and the collection went off without a hitch — but warning signs were already starting to set in. "He was relapsing by the time we collected his cells," Patel said.
Patel brought him back into the hospital for more chemo after the team collected his cells. Then he started having numbness and pain all over his body. The myeloma had spread into his skull and his spinal fluid. On an MRI, Patel could see the cancer setting roots into his nerves and spinal cord. It was just a couple weeks after they'd collected Goltzene's T cells for engineering, and Patel just had to keep the myeloma under control for a few more weeks.

"I was hopeful that cranial spinal radiation would work," she said. "I never had a patient where the radiation didn't work for at least six months."

But Goltzene kept getting sicker. It wasn't clear if he'd be strong enough to receive the CAR-T cells, which can have difficult side effects that — in rare cases — can be life-threatening. When the cells came back from the lab, Patel was getting him ready for infusion when another complication struck. A hole had torn open in his bowel.

Patel was in a bind. It seemed like all of his complications were due to myeloma, so giving the CAR-T should help. But prepping him for CAR-T would deplete his already low platelet and blood counts, making it impossible for the surgeons to operate and fix the perforated bowel if they needed to, and Goltzene was in such bad shape that Patel feared the side effects from CAR-T could be too much for him to handle.

"We had the CAR-T cells and we knew he wouldn't make it four more weeks. It was like, am I going to kill you by giving this because of how bad everything was," Patel said. "I presented his case at our CAR-T meeting, and everyone agreed to move forward because it seemed like everything was caused by the myeloma. Everyone knew it was now or never."

She sat down with Goltzene and Phuong, his wife, to explain the situation. She'd come into the hospital for the meeting. As Patel talked, Phuong began to cry, but Goltzene could barely keep his eyes open and focused. The pain had been overwhelming, and the

fatigue and pain medication was muffling his mind. He slumped in his wheelchair and just listened.

When Patel finished, she asked him, “do you know what this means?”

“Yeah,” he said. “This is unfortunate.”

They looked at each other, and Patel wept.

“I recall us having to make that decision,” Goltzene said. “Her showing that emotion just let me know that she really cared, that she was always going to try to look out for what’s best for me. I just felt gratitude towards her. Whenever we had to make a decision, I’d say, ‘look, I just trust you with the wheel. Take us wherever you think we need to go.’”

This time was no different, Goltzene said. He felt that CAR-T was the only path that might work for him. He told Patel that they should go forward with the cells. The infectious disease team was able to manage the perforated bowel with medication and antibiotics, allowing it to heal and clearing him to go forward with CAR-T. His care team at MD Anderson infused the cells in April.

They worked. Over the next few weeks, Goltzene began to feel stronger and more alert. He started looking like an entirely new man, Patel said. Goltzene didn’t even suffer from any severe side effects from the CAR-T, and he continues to be in remission. “The CAR-T has drastically reduced the myeloma in my body,” he said. “I’m really optimistic. I'm getting a little stronger every day.”

The radiation that Goltzene received to keep him alive long enough to receive the CAR-T left some scars, though. He has nerve damage that’s been stopping him from walking or using his fingers, but Goltzene will work with physical and occupational therapists soon. “For the next week or two, I’m optimistic I’ll be able to stand up and just pivot from wheelchair to the couch,” he said. “That’s my personal expectation.”

He’s looking forward to going back home “and just spending time with my family. We got a swimming pool, the boys love the swimming pool,” he said.

That extra time is something that Patel can't give all her patients just yet. It's not clear when or how the CAR-T shortage will end, but she said she's also optimistic that new technologies will start to close some of the gap.

"How do we get enough slots for everyone if we can't do it now? There's hope that people can manufacture CAR-T in two days — making it easier, faster, so you're not waiting around for bad things to happen," she said. "The field is moving towards efficiency."

That might take time, yet. But for now, she'll take the small wins. On rounds recently, Patel saw Goltzene.

"And he had facial hair," she said. "I was like, you're alive!"

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