patients responded to the treatment. It is the largest study to date to evaluate this treatment for adult patients with B cell acute lymphoblastic leukemia (ALL), a rapidly progressing form of blood cancer.

ALL is a disease that often returns, or relapses, after initial treatment with chemotherapy. At that point, patients are often resistant to additional chemotherapy and are poor candidates for bone marrow or stem cell transplants, which are usually effective only if the disease is in complete remission.

The first study of this approach, published in March 2013, treated five patients. The current study, which was published this week in *Science Translational Medicine*, treated an additional 11 patients. “This study is important because it demonstrates that this is a repeatable outcome,” says Renier Brentjens, one of the study’s senior authors. “Often when we are developing new therapies, the results for the first few patients look very positive, but the results are not repeatable with larger groups of patients.”

A New Paradigm for Treatment

The new treatment, known as targeted immunotherapy, is aimed at instructing the immune system to recognize and attack tumor cells. The approach involves removing a type of white blood cells called T cells from patients and introducing a new gene into the T cells that enables them to recognize the cancer. After the gene is transferred and expressed, the T cells are infused back into the patient, where they multiply and cause a variety of immune responses aimed at attacking the cancer cells.

Michel Sadelain, Director of Memorial Sloan Kettering’s Center for Cell Engineering and a senior author of the study, developed the technique. Over the past decade, Drs. Sadelain and Brentjens, along with Isabelle Rivière, another senior author of the study and Director of Memorial Sloan Kettering’s Cell Therapy and Cell Engineering Facility, and other Memorial Sloan Kettering researchers, have investigated this approach.

“Chimeric antigen receptors, or CARs, are a new class of drugs in oncology,” says Dr. Sadelain. “They instruct immune cells collected from the patient to identify and eliminate tumor cells. The engineered cells persist in the patient long enough to induce substantial tumor regression and eventually a complete remission, acting like a ‘living drug’ and patrolling the body in search of tumor cells to eliminate.”

The researchers report in the current study that 14 of 16 total treated patients responded to the new therapy. The majority of these patients either already had or eventually will undergo follow-up stem cell transplants. However, some patients are not able to undergo transplants because they are not well enough, and others choose not to have additional treatment.

“Transplants are still the standard of care,” Dr. Brentjens says. “But as more patients get this engineered immune therapy treatment, and not all of them are able to go on to get a transplant, we’re getting an increasing number of patients we can follow over time who we hope will remain in remission for the long-term without the transplant.”

He adds that cell-based immune therapy could eventually become the new standard of care, allowing patients to avoid transplants altogether.

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Managing Side Effects

In addition to reporting outcomes for the 16 patients, the study looked in detail at the most common side effect of the treatment, known as cytokine release syndrome (CRS). CRS occurs when the engineered T cells reach the cancerous cells and release proteins called cytokines, which the T cells use to fight the leukemia. Symptoms of CRS include high fevers, low blood pressure, and changes in mental status such as confusion or agitation.

“CRS is an indication that the treatment is working, and so far it’s been fully reversible,” Dr. Brentjens explains. “So these toxicities are not something that we want to prevent, but we want to be able to minimize and manage them.”

“It’s important to remember that we have no guidelines for this technology. It’s completely uncharted territory,” he adds. “As this treatment expands to more centers — and we’re sure that it will — other physicians will need to understand why these side effects arise and have a paradigm for how to manage them.”

“There is still much more for us to learn,” Dr. Brentjens concludes. “Right now we are basing everything we know about this treatment on only 16 patients.“

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Expanding Availability of Cell-Based Treatments

“What makes the CAR technology so attractive is the potential to apply it to a wide range of cancers,” says Dr. Sadelain. “We reported over a decade ago that a molecule called CD19 could serve as a target for CAR therapy against leukemia. This insight is validated by today’s results in B cell cancers, especially ALL. We are now exploring other molecules that likewise could be targeted by CAR therapy to treat lung, ovarian, prostate, and other cancers.”

“One important feature that distinguishes Memorial Sloan Kettering from most other academic centers is our ability to translate our conceptual innovation and preclinical modeling to bring them to first-in-man clinical trials, as was the case for this ALL study,” says Dr. Rivière. “Clinical studies like this one are made possible by a visionary commitment to establishing specialized facilities such as the Cell Therapy and Cell Engineering Facility.”

In November 2013, Drs. Sadelain, Brentjens, and Rivière co-founded a new biotechnology company called Juno Therapeutics. The Seattle-based start-up is aimed at speeding the development of novel immunotherapies for cancer.

Memorial Sloan Kettering currently has trials under way evaluating cell-based immune therapies in chronic lymphocytic leukemia, B cell non-Hodgkin lymphoma, prostate cancer, and the pediatric form of ALL.

Additional trials are planned for other types of cancer, as well as a phase II study for B cell ALL, but it is too early to say when those studies may be open to patients.

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