Chimeric Antigen Receptor–Directed Natural Killer Cells for B Cell Malignancies

New take on an experimental therapy holds promise for patients with acute lymphoblastic leukemia, chronic lymphocytic leukemia, other lymphoid cancers

By Joe Munch

Reports of remarkable response rates and long-lasting remissions are beginning to emerge from clinical trials of chimeric antigen receptor (CAR) T cells in patients with B cell malignancies. However, the promising therapy is out of reach for patients who lack sufficient T cells for CAR T cell generation or cannot afford to forgo treatment for the time it takes to generate CAR T cells.

To sidestep these barriers, researchers at The University of Texas MD Anderson Cancer Center are turning to natural killer (NK) cells to expand the use of CAR-directed therapy in patients with B cell malignancies. And starting soon is a clinical trial of CAR NK cells in patients with relapsed or refractory B cell malignancies.

Potential limitations of T cells

In CAR T cell therapy, T cells collected from a patient's blood via apheresis are brought to a laboratory,
where they are engineered to express CARs on their surfaces. The CARs increase the T cells’ ability to target certain cancer cells by enabling the T cells to recognize specific antigens the cancer cells express. The resultant CAR T cells are expanded in vitro and then infused back into the patient, where they attack and kill cancer cells that express the target antigen. Because the CAR T cells remain in the body long after they have been infused, they can protect against recurrence and result in durable remissions.

However, CAR-directed therapy with T cells has a significant drawback. “The main problem with CAR T cell therapy is that we have to use autologous T cells, and this means that we have to generate a personalized product for each patient,” said Katy Rezvani, M.D., Ph.D., a professor in the Department of Stem Cell Transplantation and Cellular Therapy, noting that autologous T cells cannot be used for CAR T cell therapy because they carry a high risk of life-threatening graft-versus-host disease (GVHD). “Taking the patient’s own T cells and engineering them to express the CAR and then expanding them and giving them back to the patient takes time, and it’s not always feasible. Sometimes the patient’s disease progresses; and sometimes the patient has had a lot of chemotherapy, so there may not be an acceptable number of T cells to generate the product.”

To avoid the potential limitations of CAR T cells, a group led by Dr. Rezvani and Elizabeth Shpall, M.D., a professor in the Department of Stem Cell Transplantation and Cellular Therapy, proposes to use NK cells instead for CAR-directed therapy.

**The advantage of NK cells**

“The beauty of NK cells is that you can give a patient allogeneic NK cells and they will not cause GVHD, like allogeneic T cells would,” Dr. Rezvani said. “Many, many patients at our center and other centers have received allogeneic NK cells for immunotherapy, and there’s no risk of GVHD.”

This simple beauty could translate into a potentially big benefit in CAR-directed therapy. NK cells from umbilical cord blood can be engineered to express CARs and then stored for use in virtually any patient. This approach would eliminate not only the need for creating a new batch of tumor-targeting cells for each patient but also the weeks-long wait that goes with doing so.

“Our argument is that using NK cells will overcome the limitation of having to make a new product for each patient, like we have to do with T cells,” Dr. Rezvani said. “We can have an off-the-shelf product that is ready to use.”

At MD Anderson, NK cells for CAR-directed therapy are harvested from cord blood specimens maintained in the institution’s Cord Blood Bank, which is led by Dr. Shpall. The cells are modified by stable transduction with a retroviral vector to introduce several new genes with specific functions into the cells’ DNA. CD19, a hallmark of B cell malignancies, increases the CAR NK cells’ specificity for the disease. IL15, which enhances cell proliferation and survival, prolongs the presence of CAR NK cells in the body; without this gene, the cells would not last more than 2 weeks after infusion.

“With the addition of IL15, you get more persistence and hopefully better therapeutic efficacy,” Dr. Rezvani said. Finally, an inducible CASP9-based “suicide gene,” whose activation by a small-molecule dimerizer induces apoptosis of the CAR NK cells, is included as a means to eliminate the cells if they are found to cause substantial toxicity.

“Non-engineered allogeneic NK cells have minimal if any toxicity, but once you engineer NK cells to express a CAR and have cytokine receptors, they may end up being toxic, which is why we need the suicide gene,” Dr. Rezvani said.

Preclinical studies of the cells have shown promising results. Compared with CAR NK cells expressing only the CD19 receptor, CAR NK cells transduced with CD19, IL15, and the CASP9-based suicide gene had significantly better proliferation in vitro and resulted in significantly greater tumor inhibition and longer survival in a murine model of lymphoma. In addition, pharmacological activation of the suicide gene efficiently eliminated the CAR NK cells both in vitro and in the murine model.

**Upcoming clinical trial**

On the basis of the promising preclinical studies, Dr. Rezvani, Dr. Shpall, and their colleagues are beginning to move their CAR NK cells into clinical trials. The first such trial will enroll patients with B cell malignancies expressing CD19 because the antigen has been successfully targeted with CAR T cells in these cancers. In the phase I/II trial, patients with relapsed or refractory B cell malignancies—including acute lymphoblastic leukemia, chronic lymphocytic leukemia, and non-Hodgkin lymphoma—will receive basic standard chemotherapy with cyclophosphamide and fludarabine before receiving CAR NK cells.

**“Our argument is that using NK cells will overcome the limitation of having to make a new product for each patient.”**

– Dr. Katy Rezvani
Dr. Rezvani said.

Dr. Rezvani anticipates that the limitations of the therapy will be manageable.

“I think the main limitations are going to be related to toxicity, based on what we can extrapolate from what’s happened with CAR T cells,” Dr. Rezvani said. CAR T cells can cause cytokine release syndrome, a condition arising from the activated T cells’ mass secretion of cytokines that, in its extreme, causes symptoms akin to those of a severe systemic inflammatory response. CAR T cells can also have neurotoxic effects. “The good news is, we have experience in managing the toxicity of CAR T cells, and we’ve incorporated that experience into our protocol with a very strict algorithm of how to prevent and manage such toxicity if we see it with CAR NK cells.”

The trial protocol has already entered the approval process, Dr. Rezvani said. She and Dr. Shpall hope to open the trial to patients at MD Anderson soon.

Dr. Rezvani said that plans are in place to use CAR NK cells targeting other hematological cancers, including multiple myeloma and acute myelogenous leukemia, as well as myelodysplastic syndrome. Using CAR NK cells to target some solid tumors is also a possibility, and preliminary data in this area are beginning to accrue.

“If the CAR NK cell approach works, I think it’s going to be game-changing because for the first time we would have an effective, off-the-shelf therapy that would be readily available to many more patients than what we are doing at the moment with CAR T cells,” Dr. Rezvani said.

A potential game-changer

Preoperative chemotherapy and chemoradiation can benefit patients with localized pancreatic cancer, but such regimens may exacerbate an already high symptom burden and diminish patients’ functional status. To maintain or improve pancreatic cancer patients’ functional status during preoperative therapy, researchers at the University of Texas MD Anderson Cancer Center are investigating an exercise program. This program may also improve the efficacy of chemotherapy.

“Patients with pancreatic cancer can rapidly get debilitated, even when their tumor burden is small,” said Matthew Katz, M.D., an associate professor in the Department of Surgical Oncology. “Unlike patients with colon or breast cancer—who can have widespread metastatic disease and still be completely functional—patients with pancreatic cancer can have a 1-cm tumor and be cachectic and profoundly ill.”

Dr. Katz and colleagues are investigating an individualized exercise program for pancreatic cancer patients undergoing preoperative chemotherapy. The researchers have already demonstrated that despite the high symptom burden, patients with newly diagnosed, potentially curable pancreatic cancer

By Bryan Tutt

Preoperative exercise program for Pancreatic Cancer Patients

Prehabilitation regimen to improve functional status during chemotherapy evaluated in clinical trials

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Nathan Parker, a graduate research assistant who is pursuing a Ph.D. in kinesiology, demonstrates the resistance tubes used for strengthening exercises in a prehabilitation regimen for patients who are undergoing preoperative therapy for pancreatic cancer.
can indeed adhere to a regimen of preoperative exercise, or prehabilitation. In addition, the researchers’ preclinical data indicate that the exercise program could increase chemotherapy efficacy. And now, an upcoming randomized trial could determine whether the program improves functional status as expected.

**Rationale for prehabilitation**

Prehabilitation has its roots in orthopedic surgery, where it was shown that preoperative exercise to strengthen the affected limb could speed postoperative recovery. In recent years, the concept has been applied to cancer surgery, with the goal of reducing postoperative complications and improving patients’ functional status so they can receive further cancer treatment (see “Prehabilitation,” *OncoLog*, September 2015).

“Data show that patients with poor performance status are less likely to do well after surgery,” said An Ngo-Huang, D.O., an assistant professor in the Department of Palliative, Rehabilitation, and Integrative Medicine. “And in a recent study of colorectal cancer patients, a program focused on nutrition, exercise, and psychology improved patients’ fitness.”

However, although exercise programs have been shown to improve some physiological outcomes, they have not been shown to improve oncologic outcomes. But this may soon change, as preclinical studies indicate that exercise can enhance chemotherapy drug delivery by improving the vasculature of pancreatic tumors.

“In most tumors, the blood vessels are very dysfunctional because they grow rapidly and never mature to become fully efficient. If you’re giving a drug that requires blood delivery to get to the tumor cells, you’re doing a better job of delivering the drug to the healthy organs than to the tumor,” said Keri Schadler, Ph.D., an assistant professor in the Department of Pediatrics. In a mouse model of pancreatic cancer, Dr. Schadler and colleagues showed that mice given moderate treadmill exercise during chemotherapy had normalized tumor vasculature and decreased tumor growth compared with control mice.

The researchers also found that tumors from mice in the exercise group had increased expression of γH2AX, a marker of DNA damage and a surrogate marker of chemotherapy delivery. “My data suggest that in addition to improving fitness, which is really important, exercise might actually be improving the chemotherapy effect by getting more drugs into the tumor,” Dr. Schadler said.

**Clinical trials**

In light of the known benefits of exercise before surgery and the potential of improved oncologic outcomes, Drs. Katz, Schadler, and Ngo-Huang—along with David Fogelman, M.D., an assistant professor in the Department of Gastrointestinal Medical Oncology, and Nathan Parker, M.P.H., a graduate research assistant in the Department of Surgical Oncology—developed an exercise program that pancreatic cancer patients could follow during preoperative chemotherapy or chemoradiation. This exercise program is based on the American Cancer Society (ACS) and American College of Sports Medicine (ACSM) guidelines for exercise for cancer survivors and is being evaluated in a recently completed pilot trial and an upcoming randomized controlled trial.

**Pilot study**

The single-arm pilot trial (No. 2014-0702) was open to patients with pancreatic ductal adenocarcinoma who were scheduled to receive preoperative chemotherapy or chemoradiation and then undergo pancreatectomy. The trial enrolled 70 patients, who were instructed to walk for at least 20 minutes at least 3 days per week and to do strengthening exercises with resistance tubes for at least 30 minutes 2 days per week. For the strengthening exercises, patients received instructional DVDs and written handouts as well as in-person demonstrations. The exercise regimen was tailored as necessary to accommodate individual patients’ limitations, and patients continued the program until their preoperative treatment ended.

To monitor patients’ progress and address any issues related to exercise, a trial staffer called each patient every 2 weeks. The phone calls helped moti-
Private patients to overcome obstacles to exercise, which include disease symptoms, feeling too sick to exercise for 1 or 2 days when treatment is administered, and sometimes being away from home for radiation therapy.

The trial’s main objective was to see whether patients are able to adhere to the regimen, and an analysis of the first 20 patients indicated success. Of these patients, 15 completed the exercise program; the other five did not participate and did not return to MD Anderson for surgery. The trial also used questionnaires and functional measures to assess patients’ performance status, and the 15 patients who completed the program maintained their performance status.

“Multiple issues conspire to make it difficult for these patients to exercise, which makes it all the more remarkable that the patients are doing it,” Dr. Katz said. “Are they having difficulty? Often, yes. But they’re doing it.”

“Anecdotally, patients love the exercise program,” Dr. Ngo-Huang said. “It involves them in their own care. And for some patients who’ve never exercised regularly, it’s motivated them to make a lifestyle change.”

Randomized controlled trial

With pancreatic cancer patients’ ability to adhere to the exercise regimen established, the researchers will soon begin enrolling patients in a randomized controlled trial in which some patients will participate in an exercise program and others will receive the standard of care (i.e., they will be encouraged to exercise and given a brochure on how to exercise safely). Patients in both study arms will be given Fitbit Zip activity trackers to monitor their daily distance walked.

The trial’s inclusion criteria are similar to those of the pilot trial except that patients with any type of pancreatic cancer can enroll. Another difference from the pilot trial is that the exercise regimen is being adjusted from 120 minutes to 150 minutes of aerobic activity per week. This modified regimen, called PancFit, more closely matches the ACS and ACSM guidelines.

The new trial’s primary objective is to compare the difference in fitness changes, as measured by 6-minute walk tests given before the start and at the completion of preoperative therapy, between patients in the exercise program and those in the control group. Secondary objectives include comparing performance status and quality of life, as measured by questionnaires, between the two groups.

Correlative studies

Most patients who complete the exercise program will go on to have their pancreatic tumors removed. Tumor specimens from these patients can provide a wealth of information about the effects of exercise on pancreatic tumors during preoperative treatment.

“I’ve analyzed tumors from patients in the pilot trial, and the results are pretty impressive,” Dr. Schadler said. “We think exercise may be causing the same type of vasculature changes in humans as in mice.”

In addition to comparing tumor specimens, Dr. Schadler will compare levels of circulating TSP-1 (thrombospondin-1) between the randomized trial’s two treatment arms. High levels of TSP-1 correlate with good prognosis in pancreatic cancer patients, and Dr. Schadler has shown that exercise increases TSP-1 levels in mice. “It’s not clear whether high TSP-1 levels simply correlate with better outcomes or actually cause better outcomes,” she said. “But if we can show that exercise increases TSP-1 in humans, it would be encouraging.”

A strong research program

A major strength of the research program is the quality of care the patients receive. “This research takes place in the context of a pancreatic surgery program that has the highest survival rate on the planet,” Dr. Katz said. “Our patients who undergo surgery have a median survival of more than 43 months, which for pancreatic cancer is a big deal, considering that median survival for patients in the United States overall is less than 20 months.”

Another strength is that the exercise research can be done in conjunction with other clinical research. “Being in the exercise program is not mutually exclusive to being in a clinical trial of investigational agents,” Dr. Katz said. “Some patients who participated in the pilot exercise trial also received preoperative immunotherapy here through another ongoing trial. We think that adding exercise to these novel therapies will yield an exponential increase in benefit with no added risk.”

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FURTHER READING


For more information about clinical trials for pancreatic cancer patients, visit www.clinicaltrials.org.
Neoadjuvant Immunotherapy for Non–Small Cell Lung Cancer

Clinical trial will evaluate immune checkpoint inhibitors in patients with operable early-stage disease

By Kathryn Hale and Bryan Tutt

About half of patients who undergo tumor resection for early-stage non–small cell lung cancer (NSCLC), the most common type of lung cancer, experience recurrence and/or progression to metastatic disease. While immune checkpoint inhibitors have been shown to benefit some patients with metastatic NSCLC, it is not known whether giving such drugs before surgery can reduce the risk of recurrence and metastasis in patients with early-stage disease. In hopes of achieving such risk reduction, a new clinical trial at The University of Texas MD Anderson Cancer Center will offer preoperative therapy with checkpoint inhibitors to patients with early-stage NSCLC.

“In trial after trial, the checkpoint inhibitors have yielded more and longer responses than standard chemotherapy for metastatic NSCLC,” said William N. William Jr., M.D., an associate professor and chief of the Head and Neck Section in the Department of Thoracic/Head and Neck Medical Oncology. “But only about 20% of these patients have a durable response to the checkpoint inhibitors. We believe that the checkpoint inhibitors could be much more effective in patients with earlier stage NSCLC who have not yet developed metastatic disease.”

Neoadjuvant immunotherapy

Dr. William is the principal investigator of the new trial (NEOSTAR), which will be among the first clinical studies of neoadjuvant checkpoint inhibitor therapy in patients with early-stage NSCLC. The trial is expected to begin enrolling patients in May/June 2017. Eligible patients are those with recently diagnosed, operable stage I–IIIA NSCLC. Patients who have received immunotherapy or chemo-radiation therapy are not eligible.

In this trial, patients will receive one or two checkpoint inhibitors before resection. All patients will receive the PD-1 (programmed cell death protein 1) inhibitor nivolumab, and some will receive nivolumab plus the CTLA-4 (cytotoxic T lymphocyte antigen 4) inhibitor ipilimumab.

“We believe,” said Boris Sepesi, M.D., an assistant professor in the Department of Thoracic and Cardiovascular Surgery and lead surgeon in the NEOSTAR trial, “that checkpoint inhibitors given during the 6-week period before tumor resection can induce a major pathological response in a substantial proportion of patients. Moreover, our hope is that this treatment paradigm can train the patient’s immune system to recognize the tumor antigens while the tumor is still present and potentially induce a durable response.” Although the ability of neoadjuvant checkpoint inhibitor therapy to produce durable responses in NSCLC patients remains hypothetical, such responses could prevent recurrences that tend to occur even when a complete tumor resection is achieved.

Blood samples will be collected during checkpoint inhibitor treatment to monitor the immune response, and the tumor size will be monitored with imaging. As in all neoadjuvant therapy, the goals are to shrink the tumor before resection and to eliminate any existing micrometastatic disease, thus yielding a better outcome for the patient by reducing the risk of recurrence and metastasis.

The NEOSTAR trial will be available only at MD Anderson. However, the trial is designed to be as patient-friendly as possible by clustering treatments, doctor visits, and tests together so that only three visits, spaced 2 weeks apart, are required before resection. After surgery, patients will be offered standard therapy appropriate for their disease, if indicated.

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Genetic Screening for Hereditary Cancer Syndromes

Genetic counseling, testing help people assess, manage cancer risk

People with a family history of certain types of cancer may face a high risk of developing cancer themselves. Genetic counseling and testing can help these people understand their risk of hereditary cancer and their options for early detection or prevention.

Hereditary syndromes

About 5%–10% of cancers are the result of inherited genetic mutations. These mutations cause what are called hereditary cancer predisposition syndromes. Not all mutations involved in hereditary cancer predisposition syndromes have been identified, but some can be detected by blood tests. Some of the more common hereditary syndromes are listed below.

**Hereditary breast and ovarian cancer syndrome** is the most common cause of inherited breast cancer. This syndrome is caused by mutations in the BRCA1 and BRCA2 tumor suppressor genes. When normal, these genes help prevent uncontrolled cell growth. However, mutations in the genes can remove their protective effect and allow cancer to develop. Women who inherit a BRCA mutation are more likely to develop breast and ovarian cancers than are women who do not carry a mutation. Men with one of these mutations face an increased risk of breast and prostate cancers.

**Lynch syndrome**, or hereditary nonpolyposis colorectal cancer syndrome, is caused by mutations in DNA mismatch repair genes. These genes normally help repair damaged cells or stop them from reproducing. But when the genes do not function properly, colorectal cancer or uterine cancer may occur at an early age.

**Cowden syndrome** is characterized by small, benign (noncancerous) growths called hamartomas on the skin and mucous membranes. People with Cowden syndrome also have an increased risk of tumors developing in the breast, uterus, and thyroid. Cowden syndrome is caused by a mutation of the PTEN gene, which controls the production of an enzyme that regulates cell growth. Mutations of this gene cause uncontrolled cell growth that results in benign or malignant (cancerous) tumors.

Other hereditary cancer predisposition syndromes include **neurofibromatosis**, leading to malignant nerve-sheath tumors; **Gardner syndrome**, leading to cancers of the gastrointestinal tract; **Li-Fraumeni syndrome**, leading to multiple types of cancer including breast cancer; and **Von Hippel-Lindau disease**, leading to cancers of the eye, brain, and spinal cord.

Genetic counseling and testing

People with two or more close relatives (parents, children, or siblings) who have had the same type of cancer may want to consider genetic testing. Likewise, some current or former cancer patients—such as those who were diagnosed at a young age, have a close relative with the same type of cancer, or have certain rare cancer types—may want to undergo genetic testing to see if their family members are at risk.

Deciding whether to be tested for an inherited cancer-causing genetic mutation can be difficult. In addition to possibly causing a psychological burden, testing is expensive and may not be covered by insurance. Genetic counselors can help guide their clients through the decision-making process and help them decide whether genetic testing is right for them.

In a genetic counseling session, the counselor meets with the client and reviews the client's family history of cancer to see if testing is appropriate. The counselor explains what the positive or negative results of the test mean. If the client undergoes testing, the counselor sees him or her afterward to discuss the options for follow-up cancer testing and preventive measures.

A positive result means the client has the inherited mutation that was tested for. Although not all individuals with an inherited mutation develop cancer, they do face a significantly increased risk of cancer and can take a more proactive approach to cancer screening. For example, a man with Lynch syndrome would need to have screening colonoscopies at regular intervals to detect and remove precancerous polyps. A woman who tests positive for a BRCA mutation could undergo more intensive screening, such as breast MRIs and earlier mammograms.

Preventive surgery is also an option for some people with hereditary mutations. For example, some women with BRCA mutations choose to undergo a bilateral mastectomy (removal of both breasts) to reduce their breast cancer risk by about 95% or removal of the fallopian tubes and ovaries to reduce their ovarian cancer risk by 80%–90%. Genetic counselors can help people weigh the pros and cons of these procedures.

Many hospitals and clinics that offer genetic testing also offer genetic counseling. For example, The University of Texas MD Anderson Cancer Center's Clinical Cancer Genetics Program offers both genetic counseling and testing to current cancer patients as well as people who are not MD Anderson patients.

— B. Tutt

FOR MORE INFORMATION

- Ask your physician
- Visit the Clinical Cancer Genetics Program online at www.mdanderson.org/departments/cgg
- Call the Clinical Cancer Genetics Program at 844-565-2361
Immunotherapy for Non–Small Cell Lung Cancer

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Precision immunotherapy

In metastatic NSCLC and other cancers, checkpoint inhibitors are not effective in all patients. One aim of the NEOSTAR trial is to determine the characteristics of tumors that respond to the checkpoint inhibitors. Such knowledge could expand the numbers of patients who benefit from these agents while avoiding exposure for patients who are unlikely to benefit.

Tumor and tissue specimens and blood samples from patients in the NEOSTAR trial will be analyzed using methods modeled after the ongoing Immunogenomic Profiling of Non–Small Cell Lung Cancer (ICON) project. “In the ICON project, we are conducting an in-depth molecular analysis of resected tumors, surrounding tissues, and blood from patients with early-stage NSCLC and integrating those findings with clinical and outcome data to develop a comprehensive immunogenomic profile of these tumors,” said Dr. Sepesi, a co-leader of the project along with Don Gibbons, M.D., Ph.D., an associate professor in the Department of Thoracic/Head and Neck Medical Oncology. “This profile will generate a list of biomarkers—mutation or aberrant expression of specific genes and proteins—and an immune profile that can be used to learn more about how immunotherapy works in NSCLC.”

The ICON project and NEOSTAR trial aim to expand understanding of the immune response to NSCLC and how it could be harnessed to fight the disease. “The ICON project and NEOSTAR trial are efforts to thoroughly characterize immunologic cell activity in and around the tumor,” Dr. William said. “Armed with this information, we can develop novel therapies that narrowly target that activity. Eventually we hope to engineer T cell receptors that target specific tumor antigens, which will zero in on the tumor with minimal systemic effects or development of resistance.”

Dr. William continued, “The way we are looking at tumors in NEOSTAR goes beyond traditional staging and histologic criteria to develop new ways of identifying individuals who respond to specific therapies and of understanding what that response looks like.” And even as researchers use immunogenomic profiling to develop future treatments, the neoadjuvant immunotherapeutic approach offered by the NEOSTAR trial may give current patients with early-stage, operable NSCLC a better chance at long-term survival.

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The NEOSTAR trial and ICON project are part of MD Anderson’s Lung Cancer Moon Shot program. For more information, visit http://bit.ly/2nKbOLF.

For more information about clinical trials for patients with lung cancer, visit www.clinicaltrials.org.