OncoLog
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Immunotherapy for Glioblastoma

Clinical trials test innovative immunotherapy approaches against brain tumors

By Bryan Tutt

Despite aggressive treatment with surgery, radiation, and chemotherapy, glioblastoma typically recurs within a few months and causes death within 2 years. In hopes of prolonging the survival of patients with newly diagnosed or recurrent glioblastoma, researchers at The University of Texas MD Anderson Cancer Center are investigating immunotherapy approaches such as immune checkpoint inhibitors, modified T cells, cord blood–derived natural killer (NK) cells, and STAT3 (signal transducer and activator of transcription 3) inhibitors.

"We see about 300 new patients with glioblastoma every year," said John de Groot, M.D., a professor in and chair ad interim of the Department of Neuro-Oncology. "And we have some exciting immunotherapy studies for these patients."

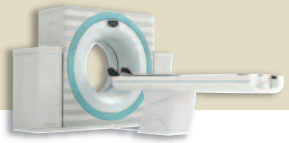
Two-photon microscopy shows interaction between GL261 glioma cells (blue), T cells (red), and macrophages (green) in the brain of a live mouse. Images courtesy of Drs. Tomasz Zal and Felix Nwajei.

Challenges and opportunities

Glioblastoma has several characteristics that impede clinicians and researchers. "Some tumors, such as lung cancer or melanoma, have high mutational loads, which result in a long list of antigens that can be targeted for treatment. But this is not the case for glioblastoma," said Amy Heimberger, M.D., a professor in the Department of Neurosurgery. On a scale of the number of mutations within various types of cancer, Dr. Heimberger said, glioblastoma falls in the middle range.

Along with a limited number of mutations, tumor heterogeneity is a hallmark of glioblastoma. Thus, there are few targets, and the same targets do not occur in all patients. "Because these tumors are heterogeneous, one drug is not going to be a home run that cures most patients," Dr. Heimberger said.

Finally, the blood-brain barrier presents a challenge to glioblastoma treatment and was once believed to prevent immune cells in the bloodstream from reaching the brain. However, research at MD Anderson and elsewhere has



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shown that such immune cells do indeed reach brain tumors, making immunotherapy an option. "It's been shown that inflammation in the brain can open up the blood-brain barrier so that immune cells can gain access to the brain parenchyma," said Tomasz Zal, Ph.D., an associate professor in the Department of Immunology.

Dr. Zal's laboratory is one of the first in the world to use two-photon microscopy, which enables researchers to visualize fluorescently stained cells deep in living tissue. Dr. Zal and his colleagues use this technology to study tumor formation and the immune response in the brains of living mice.

"Understanding the mechanisms of the immune response can help us schedule immunotherapy doses," Dr. Zal said. "Timing is critical in immunotherapy: all is dependent on when immune cells are recruited to the tumor." He added that close collaboration between MD Anderson clinicians and basic scientists enables them to explore multiple approaches to immunotherapy.

When possible, clinicians like to begin a patient's immunotherapy regimen as soon as glioblastoma is identified—and before resection. When immunotherapy is administered during this "window of opportunity" in clinical trials, the treatment's effects are studied in the surgical specimen at the time of resection.

"These window-of-opportunity trials allow us to give an immunotherapy and determine whether a sufficient number of immune cells are trafficking to the tumor and whether those immune cells are functionally able to kill the cancer," Dr. Heimberger said. "These trials are starting to reveal secrets of the tumor microenvironment and may help us identify strategies that could further enhance the immune response." The window-of-opportunity concept is exploited in two trials that are currently enrolling patients with glioblastoma at MD Anderson: one in which patients receive an immune checkpoint inhibitor and another in which patients receive autologous modified T cells.

Pembrolizumab

"In one of the most promising trials in our immunotherapy portfolio, patients with recurrent glioblastoma are given a checkpoint inhibitor before surgery," Dr. de Groot said. In this clinical trial (No. 2014-0820), patients receive two doses of the PD-1 (programmed cell death protein 1) inhibitor pembrolizumab before surgery. The patients continue to receive the drug after surgery until disease progression or unacceptable toxic effects occur.

Dr. Heimberger, a co–principal investigator of the trial along with Dr. de Groot, said, "I think there will be a subset of patients in this trial who respond to monotherapy with an immune checkpoint inhibitor, but it is likely that a combination of immune therapeutics that enhance immune targets, immune activation, and immune cells' trafficking to tumors will work best for our future patients."

Adoptive T cell therapy

Another ongoing trial (No. 2014-0899) uses autologous cytomegalovirus-specific T cells. "Almost everyone experiences cytomegalovirus infection in their lifetime, and there's a possible association between the virus and glioblastoma," Dr. Heimberger said. She added that while it is not clear whether cytomegalovirus has a role in glioblastoma formation, cytomegalovirus-specific antigens such as CMV pp65 are known to be expressed in glioblastoma.

Research led by Elizabeth Shpall, M.D., and Katy Rezvani, M.D., Ph.D., both professors in the Department of Stem Cell Transplantation and Cellular Therapy, showed that cytomegalovirus-specific T cells can home to the tumor tissue but that a large proportion of the T cells' effector function is suppressed. The researchers then developed a strategy to rapidly expand polyfunctional, highly cytotoxic virus-specific T cells. Such T cells are used in the current trial.

The trial, led by Marta Penas-Prado, M.D., an assistant professor in the Department of Neuro-Oncology, has two treatment arms in its phase II portion: one in which patients with recurrent glioblastoma begin T cell therapy before surgery and one in which patients with newly diagnosed glioblastoma begin T cell therapy after surgery and radiation therapy. In both treatment arms, patients' T cells are removed by leukapheresis. Each patient's T cells are cultured with CMV pp65 and expanded in MD Anderson's Good Manufacturing Practice and Cellular Therapy Facility, which is led by Drs. Shpall and Rezvani.

After leukapheresis, patients in both treatment arms receive dose-dense temozolomide for the first 21 days of the 42-day cycle. On day 22, the patients receive their first infusion of autologous cytomegalovirus-specific T cells. For the patients with recurrent glioblastoma, resection is performed on day 30. Patients in both treatment arms continue receiving dose-dense temozolomide and T cell infusions for a total of four 42-day cycles followed by standard-dose temozolomide monotherapy until disease progression or unacceptable toxic effects.

"Temozolomide is the standard of care, and if you time it just right—give the chemotherapy and then the immunotherapy—you get an expansion of the immune response," Dr. Heimberger said. Similar to the pembrolizumab trial, analysis of the tumors resected after treatment with temozolomide and modified T cells will help Dr. Heimberger and her colleagues to quantify the extent of that immune response and ascertain whether the immune response corresponds to treatment response.

NK cells

Allogeneic NK cells from umbilical cord blood are an attractive immunotherapy option for several reasons. First, NK cells, unlike T cells, do not require a specific antigen for activation. Second, allogeneic NK cells can produce a graft-versus-tumor effect without causing graft-versus-host disease. Also, cord blood NK cells can be stored as an off-the-shelf treatment, and their safety has been demonstrated in clinical trials for patients with myeloma, lymphoma, and leukemia.

Before researchers could design a

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Virus-Specific T Cells Treat Posttransplant Infections

Banked T cells offer "off-the-shelf" therapy for patients with BK virus, JC virus, cytomegalovirus infections after stem cell transplant

By Joe Munch

A novel approach to adoptive T cell immunotherapy holds promise for some patients who develop acute, possibly deadly viral infections after undergoing allogeneic hematopoietic stem cell transplant (HSCT).

Physicians at The University of Texas MD Anderson Cancer Center are using T cells that target BK virus, JC virus, and cytomegalovirus (CMV) to successfully treat infections in HSCT patients. The T cells were developed in the institution's Good Manufacturing Practice and Cellular Therapy Facility by Katy Rezvani, M.D., Ph.D., and Elizabeth Shpall, M.D., both professors in the Department of Stem Cell Transplantation and Cellular Therapy.

"Viral infections are major causes of morbidity and mortality in HSCT patients," Dr. Rezvani said. "We're showing that we can immediately treat some of these potentially fatal infections with banked virus-specific T cells from healthy donors."

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– Dr. Katy Rezvani

Potentially fatal infections

People with healthy immune systems may harbor BK virus, JC virus, or CMV and never experience symptoms of infection. But in people with extremely weakened immune systems—such as HSCT patients—these viruses can wreak havoc. The conditions resulting from these infections can be debilitating or even deadly, and conventional treatments to fight the infections are severely lacking.

BK virus infection can cause BK hemorrhagic cystitis, which occurs in about 20% of all HSCT patients, depending on how high-risk the transplant is. BK hemorrhagic cystitis can be very painful, and patients with the condition may develop bladder hemorrhage and/or renal failure. For years, the standard of care has been limited to supportive measures, including analgesics, continuous bladder irrigation, hyperhydration, and forced diuresis.

JC virus infection can cause progressive multifocal leukoencephalopathy (PML), a rare, demyelinating disease of the central nervous system that is marked by a sudden and severe loss of coordination and language ability. Treatment for PML is virtually nonexistent, and most patients who are diagnosed with it die within 6 months.

CMV infection can cause multiorgan disease that includes hepatitis, gastroenteritis, pneumonia, and encephalitis. Drugs to treat the infection are toxic and expensive.

The right cells at the right time

Previous efforts to use virus-specific T cells to treat viral infections in immune-deficient patients were hampered by the duration and complexity of cell production. Cell lines were generated on a patient-by-patient basis, which precluded their use in emergent situations.

"If we were to generate the T cells for each patient individually, then the patient would have to sit there for 2 weeks and suffer," Dr. Rezvani said. To overcome these limitations, Dr. Rezvani and her colleagues established a cell bank of virus-specific T cells.

BK virus–specific T cells

For BK virus–specific T cells, an in-house procedure is used to generate the cells and expand them ex vivo. Peripheral blood mononuclear cells from healthy donors are cultured with five peptides from the immunodominant capsid proteins of the BK virus (VP1, VP2, VP3, large T antigen, and small T antigen) in the presence of cytokines (interleukin-2, -7, and -5) for 10–14 days. The expanded BK virus–specific T cells are then harvested and frozen.

BK virus–specific T cells can be used to treat both BK hemorrhagic cystitis and PML because the BK and JC viruses have 95% homology. When eligible HSCT patients present with BK hemorrhagic cystitis or PML, they are given BK virus–specific T cells from the most closely HLA (human leukocyte antigen)-matched donor. The cell bank is steadily increasing its number of donors and currently has BK virus–specific T cells from 15 donors covering the most common HLA types.

"From the moment a patient comes in with a viral infection, we can administer T cells within 24 hours because all we have to do is find the best donor, thaw the cells, and give them to the patient intravenously, just like a blood or platelet transfusion," Dr. Rezvani said.

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Intensity-Modulated Proton Therapy for Oropharyngeal Cancer

Clinical trial compares outcomes of intensity-modulated proton therapy, standard radiation therapy

By Brandon C. Strubberg

Proton therapy delivers the same radiation dose to a tumor as standard radiation therapy with photons while delivering a much lower dose to surrounding tissue. But whether this reduced dose to healthy tissue results in decreased side effects for patients with head and neck cancer has yet to be proven in a randomized controlled trial. Such a trial is now under way to determine whether intensity-modulated proton therapy (IMPT) reduces adverse effects compared with photon therapy for patients with oropharyngeal cancer, one of the most common head and neck cancers.

The standard treatment for oropharyngeal cancer is intensity-modulated radiation therapy with photon beams (IMRT) used concurrently with chemotherapy. However, IMRT causes a high symptom burden because of the radiation dose delivered to surrounding healthy tissues.

"The standard photon-based radiation treatment delivers a lot of unnecessary radiation that causes collateral damage in the oral cavity, brain stem, salivary glands, and larynx," said Steven Frank, M.D., a professor in the Department of Radiation Oncology and the medical director of the Proton Therapy Center at The University of Texas MD Anderson Cancer Center. "Proton therapy, which is more precisely targeted, provides a unique opportunity to target the cancer and eliminate the unnecessary radiation in head and neck cancer patients."

Treatment plans for intensity-modulated proton therapy (left) and standard radiation therapy deliver the same treatment dose (red) to the oropharyngeal tumor, but proton therapy delivers less radiation to surrounding structures. Radiation doses in descending order are shown as red, yellow, green, and blue. Image reprinted with permission from Frank SJ. Int J Radiat Oncol Biol Phys. *2016;95:37–39.*

> **"We think proton therapy can result in better quality of life and better overall value."**
>
> **– Dr. Steven Frank**

Adverse effects

Dr. Frank said that most patients who undergo IMRT for oropharyngeal cancer experience grade 3 or 4 adverse effects. These effects include dysphagia requiring a feeding tube, severe mucositis, loss of taste leading to malnutrition with weight loss and dehydration, loss of salivary function causing difficulty in eating, dental issues, trismus, and aspiration pneumonia. Furthermore, one or more of these adverse effects develop into chronic conditions in up to 12% of patients.

In an effort to reduce the occurrence and severity of adverse effects, IMPT is now being used to treat oropharyngeal cancer. Protons deliver most of their energy at the end of their targeted path, with only a low radiation dose delivered to the surrounding healthy tissue. According to Dr. Frank, IMPT for oropharyngeal cancer typically delivers a 25-Gy-lower radiation dose to healthy tissue than does IMRT throughout the course of treatment. "How much is 25 Gy? That's equiva-

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>
> **– Dr. Steven Frank**

lent to 12,500 computed tomography scans or 5 million dental x-rays," Dr. Frank said. "So when we talk about the amount of radiation that we have the ability to eliminate during a cancer patient's treatment, it is not insignificant. Not only is it not insignificant, avoiding it can improve that patient's quality of life."

To quantify the differences in radiation doses delivered to critical structures by IMPT and IMRT, Dr. Frank and his colleagues compared the radiation plans for 50 patients with oropharyngeal cancer who received IMPT in a prior single-arm clinical trial to those for a case-matched cohort that received IMRT. IMPT resulted in significantly lower radiation doses to the oral cavity, hard palate, larynx, mandible, and esophagus and to central nervous system structures associated with nausea and vomiting. A subsequent analysis of patient outcomes found no survival differences between 50 patients with oropharyngeal cancer who received IMPT and a case-matched cohort that received IMRT, but the patients who received IMPT had lower rates of severe weight loss and feeding tube dependency.

Head-to-head trial

Dr. Frank expects the evidence in favor of IMPT to be further supported by a phase II/III clinical trial (No. 2012-0825) that is currently enrolling patients with stage III, IVA, or IVB oropharyngeal cancer. In the multicenter trial, patients are randomly assigned to receive IMPT or IMRT. Patients in both treatment arms receive the same radiation dose to the tumor (70 Gy in 33 fractions over 6.5 weeks), with or without chemotherapy as recommended by the patients' medical oncologists.

Dr. Frank, the trial's principal investigator, said the trial's primary objective is to determine whether IMPT can achieve treatment outcomes similar to those of IMRT with fewer adverse effects. Adverse effects are measured by questionnaires given at baseline and at regular intervals during and after treatment. Patients also undergo a modified barium swallow study at baseline, at the end of radiation therapy, and at regular intervals afterward to measure changes in swallowing function.

So far, more than 130 patients have been enrolled. As more centers have been added for the trial, the projected enrollment has been changed from 440 patients to 520.

"We are very excited about the trial," Dr. Frank said. "It's an opportunity to change the standard of care by eliminating unnecessary radiation."

Value of proton therapy

Dr. Frank believes the ongoing trial can help define the value of proton therapy to individual patients and the health care system as a whole. Although IMPT for oropharyngeal cancer is more expensive than IMRT, a reduced adverse effect profile could save patients and insurance companies the cost of emergency department visits, hospitalization, and treatments such as feeding tubes.

Furthermore, patients who experience fewer adverse effects will likely require less time off from work. "Head and neck tumors are highly curable and can occur in relatively young individuals who may remain in the workforce, so it is important to reduce toxicities as much as possible," Dr. Frank said. "We think proton therapy can result in better quality of life and better overall value." ■

FOR MORE INFORMATION

Dr. Steven Frank 713-563-8489

Bryan Tutt contributed to this article.

To learn more about the trial comparing proton therapy and standard radiation therapy for patients with oropharyngeal cancer, visit www.clinicaltrials.org and select study No. 2012-0825.

FURTHER READING

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Once the virus-specific T cells are given, the patient is observed for a response. If no response is apparent within 2 weeks, T cells from another donor are given.

About 85% of the HSCT patients with BK hemorrhagic cystitis who have been treated with the cells have responded to the therapy. Dr. Rezvani believes that the other patients did not respond because they had graft-versus-host disease (GVHD) and were receiving corticosteroids, which are lymphotoxic and thus kill the T cells before the cells can act. On the basis of these findings, Dr. Rezvani and her colleagues no longer administer virus-specific T cells to patients who are receiving a high dose of steroids.

"Using virus-specific T cells, we've successfully treated more than 20 patients who had BK hemorrhagic cystitis and two who had PML," Dr. Rezvani said, "One of these patients with PML, a 32-year-old woman who had a cord blood transplant, couldn't walk and couldn't talk properly when she came to our clinic. When we gave her these cells, she had an amazing response, and now she can walk and talk again. She's even back to work now, 11 months after first presenting with PML; and the virus is no longer detectable in her blood or cerebrospinal fluid." Given that PML is almost universally fatal, the patient's response to the therapy was particularly encouraging, Dr. Rezvani said.

Although the BK virus–specific T cells are most often used in the post-transplant setting, Dr. Rezvani said that she has also used them to treat leukemia patients who develop BK hemorrhagic cystitis after chemotherapy. She noted that, because patients must be highly immunosuppressed to develop the condition, BK hemorrhagic cystitis is rare in non-transplant settings.

CMV-specific T cells

Unlike BK virus–specific T cells, which must be cultured, manipulated, and expanded over a dozen days or more, CMV-specific T cells, which are substantially more abundant than BK virus–specific T cells in healthy individuals, can be generated in a matter of hours. Donor cells are stimulated with a mix of peptides of the virus's immunodominant proteins overnight. The cells start secreting interferon gamma, which allows their detection and isolation by a cytokine capture device. The T cells are immediately harvested and infused into the patient, where they start growing and mediate an antiviral response. So far, the response rate to CMV-specific T cells has been greater than 80%, and 20 patients have been successfully treated.

> **"Where we used to have these patients in the hospital for weeks on end, now we give them these T cells, and most patients respond within a week."**
>
> **– Dr. Katy Rezvani**

Potential limitations

Dr. Rezvani said that although treatment with the virus-specific T cells has been safe and effective overall, it is not without potential limitations.

"There's always the theoretical risk that T cells from an allogeneic source could increase the risk of GVHD, although we haven't noticed a higher-than-average incidence of GVHD in the patients we've treated," Dr. Rezvani said. "There's also a theoretical risk that T cells from an allogeneic source could contribute to graft rejection, but we haven't seen any cases of this in our patients."

There is also a small risk that a good donor match would be unavailable or that even well-matched cells may not work, as was the case in patients who were receiving corticosteroids for GVHD.

Future directions and broader applications

The next step, Dr. Rezvani said, is to make virus-specific T cells available to additional patients. "At the moment, this is a boutique strategy at major transplant centers that have the technology to modify T cells, but we'd like to see the treatment become available to patients at other institutions," she said. She also mentioned that steps are being taken to make virus-specific T cells more effective.

Other uses for virus-specific T cells are also being explored. For example, CMV-specific T cells are being used in combination with temozolomide in a clinical trial to treat recurrent glioblastoma, which expresses CMV antigens (see "Immunotherapy for Glioblastoma," p. 1). Dr. Rezvani said that early findings suggest that virus-specific T cells could also be used to treat other cancers in which viruses play a role (e.g., human papillomavirus–associated head and neck cancers). More broadly, Dr. Rezvani pointed to the work of Ala Abudayyeh, M.D., an assistant professor in the Department of Nephrology, who is investigating the use of BK virus–specific T cells to prevent graft rejection in kidney transplant patients.

Dr. Rezvani predicts that off-the-shelf, virus-specific T cells will become commercially available within a few years but will likely be expensive. Currently, the in-house generation of the virus-specific T cells used at MD Anderson is supported by the institution's Moon Shot Program, so there is no cost to the patient. With this support, Dr. Rezvani said, she continues to see the therapy elicit dramatic responses in HSCT patients with infections that once were debilitating and deadly.

"Where we used to have these patients in the hospital for weeks on end, now we give them these T cells, and most patients respond within a week of receiving them," Dr. Rezvani said. "The therapy has made a huge difference in these patients' quality of life." ■

FOR MORE INFORMATION

Dr. Katy Rezvani 713-794-4260

Lung Cancer Screening

Low-dose computed tomography can detect lung cancer early

Lung cancer is the leading cause of cancer-related death in the United States for both men and women. In fact, the American Cancer Society estimates that more than 155,000 people will die from lung cancer this year. One of the reasons lung cancer is so deadly is its lack of early symptoms: most cases go unnoticed until the disease has spread beyond the lungs, making treatment less effective.

The good news is that lung cancer screening with low-dose computed tomography (CT)—which delivers less than a quarter of the radiation dose of diagnostic CT—can find tumors in the lungs before the cancer spreads to other parts of the body. Clinical trials at The University of Texas MD Anderson Cancer Center and elsewhere have shown that low-dose CT screening, compared with a standard chest x-ray, reduces the risk of dying from lung cancer by 20% in people at high risk of the disease.

Risk factors and screening guidelines

Cigarette smoking is the most common cause of lung cancer, and the disease tends to develop in older adults. With these risk factors in mind, the clinical trials of low-dose CT screening tested its effectiveness in people who were heavy smokers over a long period. The trials' results led to the current recommendation for annual lung cancer screening for individuals who:

- are between 55 and 74 years old,
- currently smoke cigarettes or have quit within the past 15 years,
- have a smoking history of at least 30 pack-years (30 pack-years = 1 pack of cigarettes per day for 30 years, 2 packs per day for 15 years, etc.), and
- are in reasonably good health.

Some people who do not meet these guidelines may be eligible for lung cancer screening at MD Anderson in a clinical trial (No. 2013-0609) that extends the criteria to include individuals as young as 50 years or older than 74 years as well as people with a 20 pack-year smoking history and one or more additional risk factors. These risk factors include exposure to radon or other toxins, a history of other cancers or lung disease, or a family history of lung cancer.

It's important to remember that if you have symptoms that are concerning, you don't need to meet screening criteria to be evaluated. No matter what your specific age or smoking history, you should see your doctor if you experience symptoms such as a cough that won't go away, infections that don't get better, unexpected weight loss, voice change, or chest pain.

Insurance and planning

If you meet the guidelines listed above, your medical insurance or Medicare may cover lung cancer screening. Medicare requires that patients have a written order from their physicians and undergo counseling about the potential harms and benefits of screening.

Your doctor may be able to help you find a facility in your area that offers lung cancer screening. In the Houston area, you can be screened at MD Anderson's main campus in the Texas Medical Center or at MD Anderson's location in Sugar Land.

Your screening appointment

Like most centers that provide low-dose CT screening for lung cancer, MD Anderson offers counseling sessions before screening so that you understand the potential harms and benefits of screening. During this session, the counselor explains that an abnormal finding does not necessarily mean you have cancer. Abnormal findings may require careful watching with another CT scan in a few months; or another type of test, usually a needle biopsy, may be done to tell whether a lesion seen on CT screening is cancerous.

The low-dose CT scan takes only a few minutes and does not require any contrast liquid to be swallowed or injected. Patients and their referring physicians receive the results within a couple of business days, along with information about any follow-up tests that may be needed.

If you are a current or former smoker with a high risk of lung cancer, talk to your doctor about lung cancer screening. It's also important to remember that lung cancer screening is not a substitute for quitting smoking. The best thing that you can do to avoid dying of lung cancer is to quit smoking and to stay tobacco free. ■

– B. Tutt

FOR MORE INFORMATION

- *Talk to your physician*
- *Call MD Anderson's Lung Cancer Screening Clinic at 888-774-3020, 877-632-6789 (Medical Center), or 281-566-9012 (Sugar Land)*
- *Visit MD Anderson's Lung Cancer Screening Clinic at http://bit.ly/2jRAonQ*
- *Visit MD Anderson's Tobacco Treatment Program at http://bit.ly/2lgV4H5*
- *Visit the American Lung Association at www.lung.org*

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Immunotherapy for Glioblastoma

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clinical trial of cord blood–derived NK cells in patients with glioblastoma, they needed to know whether glioblastoma patients' own NK cells trafficked to the tumors. Drs. Rezvani and Heimberger studied NK cells in specimens from resected glioblastomas and found that NK cells reach tumors but become dysfunctional in the tumor microenvironment.

Dr. Rezvani and her group performed in vitro studies to find the reason for NK cell dysfunction. "When we cultured healthy cord blood NK cells with glioblastoma cells together, the NK cells were active at first," Dr. Rezvani said. "But after a while the glioblastoma cells induced dysfunction in the NK cells, and this dysfunction was mediated through tumor growth factor [TGF]-β." Further, the researchers found that blocking TGF-β prevented glioblastoma-induced NK cell dysfunction.

As a result of these findings, a clinical trial of cord blood NK cells combined with a TGF-β inhibitor for glioblastoma patients is expected to open later this year. Dr. Penas-Prado will be the principal investigator. The NK cells for the trial will be expanded in the Good Manufacturing Practice and Cellular Therapy Facility from cord blood units provided by MD Anderson's cord blood bank, which is led by Dr. Shpall.

Other research

In another trial expected to open soon, patients with glioblastoma will receive WP1066, a STAT3 inhibitor developed at MD Anderson by Waldemar Priebe, Ph.D., a professor in the Department of Experimental Therapeutics. "This drug can get past the blood-brain barrier and has activity against the cancer itself as well as immunological activity," said Dr. Heimberger, the trial's principal investigator. "Almost all mechanisms of tumor-mediated immune suppression tie into STAT3."

In addition to the immunotherapy trials specifically for patients with brain tumors, patients with glioblastoma often are eligible to receive new immunotherapy agents in clinical trials that are open to patients with any type of solid tumor through the Department of Investigational Cancer Therapeutics. "These trials that are open to patients with all sorts of tumors are a nice opportunity for our patients," Dr. de Groot said. "And sometimes results from those trials will lead us down an avenue to develop an agent specifically for patients with glioblastoma."

Dr. de Groot and his colleagues are hopeful that their research will clarify the role of immunotherapy in the multimodal treatment of glioblastoma and ultimately extend survival for their patients. ■

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