understand mechanisms of antitumor immunity.

The scientists also evaluated their approach by studying a different group of 173 at-risk individuals who were tracked for up to 20 years; 44 developed HCC. Wang and colleagues tested blood samples collected before diagnosis for exposure to the 61 viral strains. The results suggest that this method of testing could uncover a patient’s cancer a median of 8.8 years earlier than conventional screening techniques. “This is a proof-of-concept study,” Wang says. “The real test,” he adds, will be to evaluate whether the method can reduce mortality in a randomized clinical trial.

Researchers who weren’t connected to the study are enthusiastic about the prospects for viral profiling. Augusto Villanueva, MD, PhD, of the Icahn School of Medicine at Mt. Sinai in New York, NY, says that the approach is immunologically sound and praises its novelty. “It’s a breath of fresh air,” he says. A clinical trial now needs to determine whether it allows earlier detection of HCC, he says.

Jonathan Schwartz, MD, of the Montefiore Medical Center at Albert Einstein College of Medicine in New York, NY, adds that “if this could be validated prospectively, it could be a game changer” for HCC screening.

—Mitch Leslie

COVID-19 Challenges Status Quo for Cancer Care

Due to the COVID-19 pandemic, oncologists have had to balance patients’ need for treatment with the risk of contracting the disease, sometimes prompting them to adjust standard treatment and/or rethink its timing. Further complicating the situation, many hospitals have limited surgeries when COVID-19 cases surge and a surgical backlog once cases decrease, requiring tough decisions about the timing of operations.

Several organizations have published recommendations to help with these decisions. But Daniel Spratt, MD, of the University of Michigan School of Medicine in Ann Arbor, notes that such guidelines are typically developed for specific cancers, making it difficult to determine which surgeries should take priority or how to use other shared hospital resources.

To aid in decision-making, Spratt and his team developed oncCOVID (see http://onccovid.med.umich.edu). The tool—linked to multiple large cancer registries and the Johns Hopkins COVID-19 dashboard—assesses more than 40 factors, including patients’ type and stage of cancer, age, preexisting conditions, geographic location, and the potential length of the delay. It then estimates the risk associated with delayed versus immediate treatment. “The motive behind oncCOVID is to integrate this massive amount of data into a quantitative estimate” so that patients can receive personalized care during the pandemic, Spratt explains.

Hospitals have also developed strategies for determining how to alter treatment to minimize hospital visits without compromising care. At Dana-Farber Cancer Institute in Boston, MA, for example, Ann Partridge, MD, MPH, and her colleagues developed guidelines for breast cancer care (available at www.dana-farber.org/covidmd). “Our principles were to assure [positive] long-term clinical outcomes for patients with breast cancer, minimize the risk of infection or exposure among patients and staff, avoid immunosuppression, and preserve vital resources within the healthcare system,” Partridge explains.

In practice, when Dana-Farber postponed nonurgent surgeries due to COVID-19, Partridge used hormone therapy in patients with breast cancer awaiting surgery, a strategy often used in higher-risk situations. Partridge says they were careful about choosing which treatment regimens to adjust, relying on data from patients with advanced disease: “We didn’t do anything crazy.”

Stephanie Wethington, MD, of Johns Hopkins University School of Medicine in Baltimore, MD, made similar decisions to delay surgery in her patients. For example, she prescribed hormone therapy for some patients with endometrial cancer so that they could delay a hysterectomy—an accepted, although less common, approach. She also recommended neoadjuvant chemotherapy for patients with ovarian cancer and rescheduled surgeries for precancers and early-stage, less-aggressive malignancies.

Vor Nets $110m to Make Anti-CD33 Drugs Safer

Vor Biopharma secured $110 million in July to move its lead stem-cell therapy into clinical testing. The financing—added to $42 million raised last year—will support first-in-human trials of VOR33, an engineered cell product that employs CRISPR/Cas9 to inactivate CD33 from healthy donor hematopoietic stem cells (HSC).

The hope is that patients with high-risk acute myeloid leukemia (AML) who receive VOR33—manufactured for each individual—will better tolerate therapies that destroy cells expressing
CD33, an antigen found in abundance on leukemic blasts in most patients. “We think a transplant like ours only improves the treatment possibilities for patients, particularly those susceptible for relapse,” says Vor CEO Robert Ang, MBBS, MBA. The goal is to make the company’s gene-edited HSCs a “central hub upon which you can then build a treatment system in AML and beyond,” says Ang, adding that “there is no reason why you would use an ordinary transplant.”

The company aims to launch first-in-human trials next year to evaluate VOR33 in combination with gemtuzumab ozogamicin (Mylotarg; Pfizer). An antibody–drug conjugate that combines a CD33-targeted antibody with an antitumor antibiotic called calicheamicin, gemtuzumab ozogamicin is the only approved CD33-targeted therapy on the market. Several others are in various stages of clinical development. Yet, because some normal cells in the bone marrow, liver, and elsewhere also express the antigen, off-target toxicities, such as prolonged neutropenia and thrombocytopenia, continue to plague gemtuzumab ozogamicin and other CD33-directed agents.

“The major hurdle and obstacle has been the toxicity to the normal hematopoietic cells,” says Hans-Peter Kiem, MD, PhD, of the Fred Hutchinson Cancer Research Center in Seattle, WA, who serves on Vor’s scientific advisory board.

VOR33 might circumvent these safety problems. By reconstituting the immune system with CD33-deficient HSCs, the therapy could transform CD33 from a shared antigen into a leukemia-specific one. Because the myeloid receptor seems nonessential to normal blood formation, the approach could protect healthy tissue from CD33-guided agents without compromising the engraftment capacity or hematopoietic function of the altered cells.

Vor’s scientific founder, Siddhartha Mukherjee, MD, DPhil, and his colleagues at Columbia University Medical Center in New York, NY, showed as much last year (PNAS 2019;116:11,978–87). They injected AML cells and CD33-ablated stem cells into mice and then administered allogeneic CD33-directed chimeric antigen receptor (CAR) T cells or gemtuzumab ozogamicin. In both scenarios, the mice experienced full hematopoietic repopulation followed by complete disease remission without any noticeable side effects.

Two other groups—one co-led by Saar Gill, MD, PhD, of the University of Pennsylvania Perelman School of Medicine in Philadelphia, the other consisting of Kiem and his colleagues—individually reported similar CD33-inactivating strategies in HSCs that protected engrafted cells from complementary targeted therapies while leaving diseased cells vulnerable to attack (Cell 2018;173:1439–53; Leukemia 2019;33:762–808).

Gill’s group focused on CAR T cells because they offer the most potent depletion of CD33-expressing cells—and he worries about whether trials involving gemtuzumab ozogamicin will adequately prove the full potential of CD33-lacking HSCs. “To demonstrate the concept in human beings,” he says, “you need something that is as powerful as CAR T cells to actually induce that really profound CD33-specific perturbation of the system.”

Ang agrees, which is why Vor is looking to develop its own anti-CD33 CAR T-cell therapy. But for now, using gemtuzumab ozogamicin “is a way that we can move into the clinic rapidly,” and ensure the VOR33 cells can engraft and avoid a CD33-directed onslaught administered soon after the cell transplant. The trial will also assess whether gemtuzumab ozogamicin, which is typically given only before a transplant or following relapse, can prolong relapse-free survival in VOR33-recipient patients.

Vor scientists are additionally looking beyond CD33 to other antigens on cancer cells that could be deleted in HSCs, either alone or in combination, without harming normal hematopoietic function. (These could include CD123 and CLL1, according to Vor’s patent filings [https://patents.google.com/patent/us20200093865a1/].) “There’s a surprising amount of redundancy built into the system,” says Ang, “and molecules that you would expect to be really important may well not necessarily be.” —Elie Dolgin
Vor Nets $110m to Make Anti-CD33 Drugs Safer


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