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At Last, a Brightening Outlook for Chronic GVHD

BY MICHELLE PERRON

Although the safety and efficacy of allogeneic hematopoietic transplants for certain hematologic cancers have been improving for more than a decade, the oncology community has continued to struggle with the burdensome complication of graft-versus-host disease (GVHD).

"It is sobering to say that our practice standards of prevention and treatment haven't changed fundamentally since the early 1980s," said Steven Z. Pavletic, MD, MS, senior clinician in the Experimental Transplantation and Immunology Branch of the NCI Center for Cancer Research, where Pavletic heads the Graft-Versus-Host and Autoimmunity Section.

CME Article

But thanks to an academic and clinical consortium focused on steering a new course, "… we are entering an era of

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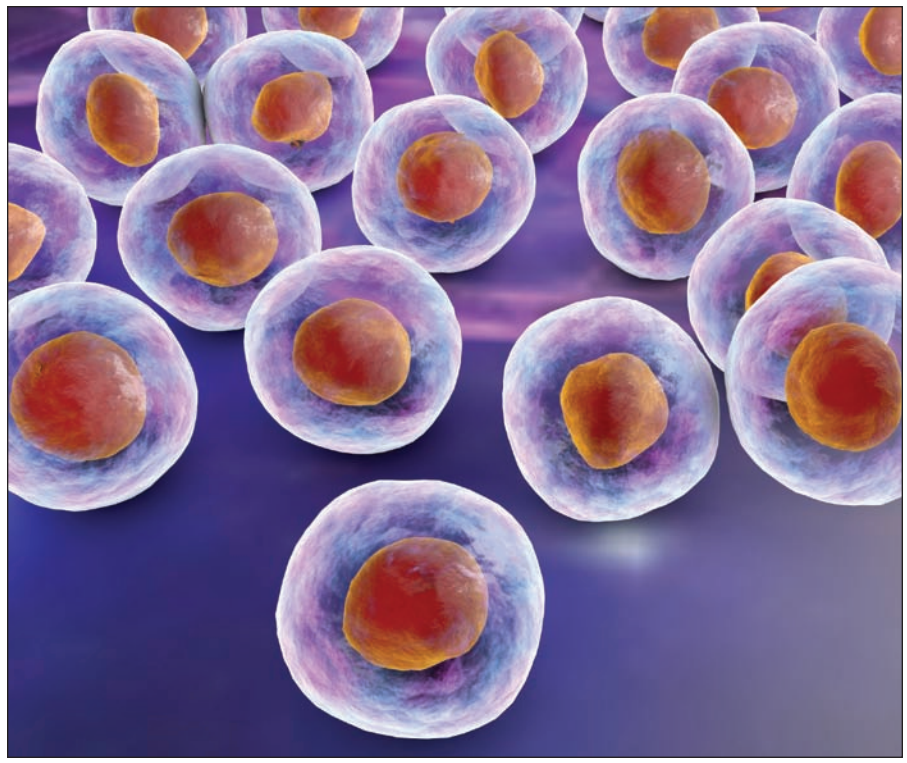

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Genome Editing: Identifying Molecular Mechanisms in Cancers

BY VALERIE NEFF NEWITT

Just below the toe of Italy's boot lies the island of Sicily. It was in the small eastern village of Furci Siculo that Andrea Ventura, MD, PhD, now an associate member in the Cancer Biology and Genetics Program at Memorial Sloan Kettering Cancer Center, New York, N.Y., first found his love of scientific discovery. Today, Ventura's research applies new genome-editing technologies to study non-coding RNAs, identify the molecular mechanisms underlying cancers, recreate mutations in mouse models, and ultimately help find new drug targets.

"As a child, I loved learning about science," recalled Ventura, whose father was a cardiologist and the village physician. "When I became a little bit older, I was exposed to the idea that a single, nearly invisible cell somehow knows how to make a person. It is still one of the most

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Trial Shows Durable Complete Responses in Adults With r/r DLBCL

Findings from an interim analysis of the multi-center phase II JULIET study (NCT02445248) of CTL019 (tisagenlecleucel) in adult patients with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) were presented at the International Conference on Malignant Lymphoma meeting, held June 14-17 in Lugano, Switzerland (*Abstract 7*). The global, pivotal study showed a 3-month overall response rate (ORR) of 45 percent (23 of the 51 patients evaluated), with 37 percent achieving a complete response (CR) and 8 percent achieving a partial response (PR), respectively. CR remained stable from 3 months through data cutoff among the patient group.

"The overall response rate seen in this early analysis is impressive for these heavily pre-treated patients with relapsed/refractory DLBCL who have limited treatment options," said JULIET lead investigator, Stephen Schuster, MD, Professor of Hematology/Oncology in the Perelman School of Medicine at the University of Pennsylvania and Penn's Abramson Cancer Center, Philadelphia. "The goal for these patients is achieving durable response. The most promising aspect of these data is that, at the time of this interim analysis, all patients with complete response at 3 months have remained in complete response."

JULIET is the first multi-center global registration study for CTL019 in adult patients with r/r DLBCL and the second global CAR T-cell therapy trial, following the ELIANA study (NCT02435849) of CTL019 in pediatric and young adult patients with r/r

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developing targeted therapies for GVHD. There is lots of excitement, and for good reason," he told *Oncology Times* in a recent interview.

The GVHD Challenge

Each year, about half of patients who receive allogeneic hematopoietic transplants develop GVHD. This complication occurs in two forms, acute and chronic. The acute form is mediated by the infusion of alloreactive donor T cells, Pavletic explained, as the immune system attacks what it senses as foreign cells. Affected patients develop rashes, nausea, vomiting, and diarrhea. Systemic management resolves GVHD in a high percentage of patients.

The chronic form of GVHD has different and more disabling complications. It most commonly evolves 6-12 months after transplant and lasts an average of 3 years, Pavletic said. Chronic GVHD is a multi-organ assault by the donor immune system that causes skin thickening, rashes, contractures, eye dryness, mouth dryness, genital tract dryness, liver damage, infections, and, potentially, organ failure.

"We had to look at chronic GVHD as an autoimmune disease we had created," he explained. "We are doing more transplants, better transplants, and the new complication of chronic GVHD was happening too often in these survivors. A decade ago we had no standardized tools to diagnose it, stage its severity, and measure therapy response."

Pavletic and colleagues at the NCI Center for Cancer Research developed an intramural research program to address the complicated challenges presented by chronic GVHD. The program features a multidisciplinary clinic that involves eight intramural institutes and five departments at the NIH clinical center. The program staff studied clinical presentations, developed assessment tools, and initiated a national network of transplant centers and stakeholders.

Their work led to a first NIH consensus conference in 2005, where researchers and clinicians proposed major changes in the diagnosis, classification, and grading of chronic GVHD (*Biol Blood Marrow Transplant* 2005;11(12):945-956). Rather than focus on the customary 100 days after bone marrow transplantation as the dividing line between acute and chronic GVHD, the new consensus criteria invoked the diagnostic characteristics of the syndrome in order to classify them. The manifestations (dermal, oral, hepatic, ocular, respiratory, gastrointestinal, and genital) occurring any time post-transplant are now considered diagnostic of chronic GVHD. The consensus conference also produced a new grading of the severity of GVHD that assigns a score for each involved organ, with attention to functional impairment. The result was a global summary score (mild, moderate, or severe) that considers the number of organs involved and the severity of the condition of those organs.

"This led to better measuring and better language, and it allowed us to pursue clinical trials to address this problem," Pavletic said of the consensus conference. "Prior to this, no single drug company wanted to work on this kind of disease. There were no standards for the disease measurement until this point. We had a second consensus conference in 2014, and by that time everything was evidence-based. By then the transplant community had gathered data and conducted research. These criteria became validated. These papers have been by now referenced more than 3,500 times in the peer-reviewed literature."

The Fast Track

The development of standards for diagnosis, therapy response, and supportive care treatment of chronic GVHD attracted more scientific attention to the need to improve outcomes, and particularly important was the interest of pharmaceutical companies.

Soon after the second NIH consensus conference, researchers began to focus on potential chronic GVHD applications for ibrutinib, a targeted therapy with an existing indication for certain blood cancers. Ibrutinib inhibits the function of Bruton's tyrosine kinase and is used in the treatment of mantle cell lymphoma, chronic lymphocytic leukemia, and Waldenström's macroglobulinemia.

A 2014 study reported that treatment with ibrutinib alleviated symptoms in mouse models with GVHD that was resistant to corticosteroids. These findings laid the foundation for human trials of ibrutinib for potential use in chronic GVHD. At the American Society of Hematology annual meeting in December 2016, researchers released findings of a small clinical trial of ibrutinib treatment for 42 patients with chronic GVHD (*Blood* 2016; 128(22):LBA-3). Patients in the trial had previous blood cancers and had developed symptoms of chronic GVHD after receiving allogeneic transplants. All subjects had received standard GVHD treatment with corticosteroids but continued to experience symptoms.

After treatment with ibrutinib, two-thirds of the patients experienced improvements in GVHD symptoms. Importantly, the symptoms completely resolved in 21 percent of these patients, and the symptom relief lasted for 5 months or longer in many of them. Based on these findings, the FDA issued Breakthrough Therapy status for ibrutinib in June 2016.

"The Breakthrough Therapy designation is for new promising agents that have novel mechanisms tailored to unmet needs," Pavletic explained. "Currently, no single agent has an FDA indication for any form of GVHD. This was a major reflection of our communal 10-year effort."

Researchers are now conducting a phase III clinical trial of ibrutinib to treat GVHD, with focus on its potential use as initial therapy rather than for patients who already have developed treatment resistance. According to published reports, the companies plan to file for regulatory approval of a GVHD indication for ibrutinib this year.

"The hope is that this new drug can help remove the need for toxic therapies," Pavletic said. "For 10 years we have studied, and we have identified a better understanding of different points where we can block T-cell and B-cell signaling. We know that we have new molecules that allow us to intervene in much safer ways.

"Ibrutinib is the first but it is not the only potential new treatment," Pavletic continued. "Studies are being pursued at a much faster pace than ever (*Leukemia*. 2017;31(3):543-554). We would like better frontline therapy. Maybe we can eliminate steroids as a standard and move on to something else."

Although great strides have been made in GVHD management, Pavletic views the future with caution, emphasizing a need for more researchers and more financial support. "We are becoming limited by a lack of clinical investigators and a lack of funding," he said. "We need the capability to do clinical trials as a community. Doctors cannot solve this, the government cannot solve this, and insurance companies cannot solve this, and clinical research teams are profoundly underfunded. Everyone must sit around the table to move things forward. Patients and advocacy groups have to push this, too." OT

Michelle Perron is a contributing writer.

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Learning Objective for This Month's CME Activity: After participating in this CME activity, readers should be able to describe major changes in the diagnosis, classification, and grading of chronic graft-versus-host disease (GVHD).