A new three-drug combination used to treat multiple myeloma may be effective as a front-line therapy for newly diagnosed patients, according to a study led by the University of Michigan Comprehensive Cancer Center.

The drug combination includes carfilzomib, a novel proteasome inhibitor, combined with lenalidomide and low-dose dexamethasone. This is the first study to look at carfilzomib as a front-line treatment of patients with myeloma.

Initial results of the Phase I study were presented at the American Society of Hematology Annual Meeting and Exposition in December. The study was one of only two myeloma abstracts featured as part of the Best of ASH presentation.

“This combination treatment appears to deliver everything we expected and more. We have seen no neurotoxicity and fantastic efficacy — the best reported to date,” says study author Andrzej Jakubowiak, M.D., Ph.D., director of the U-M multiple myeloma program.

The study, which still is accruing participants, has enrolled 31 people to date. All patients had at least a partial response, and a significant portion had complete or near-complete response. Responses were rapid, and the depth of response continued to improve with additional treatment. Of patients who completed eight cycles of therapy, more than two-thirds achieved a complete response. These response rates appear to be higher than those achieved by the best current regimens in newly diagnosed multiple myeloma.

After a median follow-up of six months, all patients were alive with no progression of their cancer.

Researchers found that the three-drug combination, called CRd, was well-tolerated, with few serious side effects. Most notably, peripheral neuropathy was infrequent and mild with this treatment. This side effect typically limits extended use of currently available multiple myeloma treatments and is often the reason patients discontinue a therapy.

“We can achieve a higher proportion of deeper responses because there are fewer toxicities, giving us the ability to keep using this therapy longer. Deepening response for people with complete response is very important,” Jakubowiak says.

“This combination treatment appears to deliver everything we expected and more.”

Andrzej Jakubowiak, M.D., Ph.D., Director of the Multiple Myeloma Program

continued on back page
IN DIRE CIRCUMSTANCES, AN EXTRAORDINARY OPTION:
U-M ECMO TREATMENT MARKS 2000TH PATIENT MILESTONE

Valerie Munguia-Bryan and Mario Bryan knew for months that one of their twin babies would be born with a devastating congenital defect. But they refused to give up hope.

The Saginaw couple was referred to the U-M Health System by their hometown physician because of U-M’s expertise in repairing difficult congenital defects and for heart-lung support technology known as extracorporeal membrane oxygenation, or ECMO. Doctors expected the couple’s newborn would need to be placed on ECMO to be kept alive from birth and through surgery.

ECMO was developed in the 1970s by U-M surgeon Robert Bartlett, M.D., now a professor emeritus. The technology — described by some of Bartlett’s colleagues as “extraordinary” — does the work of a patient’s failing heart and lungs for a period of weeks, sometimes months. That’s often long enough for the heart and lungs to rest and recover, increasing the patient’s chance of survival.

“He is a fighter, he will be victorious.”

The technology has spread worldwide, with more than 40,000 cases treated and more than 24,000 lives saved. ECMO also has the extraordinary legacy of diminishing mortality in conditions where patients used to have no chance of survival.

Manny and Victor Bryan were born Nov. 1 at U-M’s C. S. Mott Children’s Hospital. Manny was born healthy. As expected, Victor’s lungs were so underdeveloped that he was placed on ECMO immediately following birth.

The following day, he was taken to surgery to repair his prenatally diagnosed congenital diaphragmatic hernia — to fashion a new diaphragm and to move his stomach, liver and intestines out of the upper cavity of the chest, where they were pushing up against the heart and lungs.

Infants born with a congenital diaphragmatic hernia often have respiratory problems, with the severity varying by case from mild to life-threatening. In Victor’s case, it was life-threatening, so much so that Victor had two runs with ECMO. He is now recovering from a second surgery to close his abdomen.

“He is a fighter,” says his mother Valerie, who chose Victor’s name after her eye was caught by a University of Michigan poster invoking the school’s Hail to the Victors fight song. “He will be victorious.”

Victor would not be alive today were it not for ECMO, said Ronald Hirschl, M.D., Surgeon-in-Chief and Section Head of Pediatric Surgery at U-M’s Mott Children’s Hospital and Victor’s surgeon.

“He is a fighter,” said his mother Valerie, who chose Victor’s name after her eye was caught by a University of Michigan poster invoking the school’s Hail to the Victors fight song. “He will be victorious.”

Victor would not be alive today were it not for ECMO, said Ronald Hirschl, M.D., Surgeon-in-Chief and Section Head of Pediatric Surgery at U-M’s Mott Children’s Hospital and Victor’s surgeon.

“Victor had almost no diaphragm, he had small lungs, pulmonary hypertension, and blood was not going through
his lungs…. He needed the ECMO badly,” says Hirschl. “He is a perfect example of a child who wouldn’t be here today were it not for ECMO.”

Victor has become a special baby for other reasons. He is the University of Michigan’s 2000th patient to be placed on ECMO.

The milestone is one that was watched closely by the team of doctors, researchers, nurses and administrators who run the ECMO program.

“The next time I see Dr. Bartlett, I want to give him a big hug for saving my baby.”

While the numbers worldwide far exceed 2,000, U-M is where the treatment was anchored, grew, became refined and developed into what it is today. U-M is the place where thousands of doctors and nurses continue to train to bring this technology to their own hospitals.

It is to U-M that the most difficult cases continue to come — not only for U-M’s depth of knowledge in ECMO technology and care of patients, but for life-saving programs that work in conjunction with ECMO. These include Survival Flight, which flies the sickest patients from around the country on transportable ECMO technology, and the Fetal Diagnosis and Treatment Center, which identifies problems that can be treated from prior to birth and after.

“Victor is a very special baby,” says Bartlett, who retired from clinical practice in 2005 but continues research to perfect the ECMO technology. “We can’t wait for him to join his brother Manny at home soon.”

Bartlett says the future of ECMO after this 2000th patient milestone is brighter than ever. His lab continues to work on the development of artificial organs and surfaces to replace plastic tubing currently used to eliminate the need for blood thinners, which remains one of the biggest drawbacks of ECMO technology.

That breakthrough is just a few short years away. “We are very close,” says Bartlett.

Victor shares a special legacy with the first successful ECMO baby, now an adult woman whose name is Esperanza, or “Hope” in Spanish.

Esperanza’s mom gave birth to her in California 35 years ago.

In the country illegally, the frightened mom left her baby orphaned in the California hospital where Bartlett worked at the time. Her life was saved by ECMO. Esperanza was later adopted by a local family. She is now married with children and living in Missouri.

The ECMO team has been not-so-quietly cheering for Victor as he grows and overcomes hurdles. Nurses readily volunteer to hold his twin brother Manny every time Valerie visits Victor at Mott’s Neonatal Intensive Care Unit. They will cheerfully admit they’re in love with the infants.

Recently, Valerie had the chance to meet Bartlett, who came by the NICU to get a glimpse of Victor.

She can’t wait to meet him again to fix one thing she regrets not doing earlier.

“The next time I see Dr. Bartlett, I want to give him a big hug,” she says. “For saving my baby.”

FOR MORE INFORMATION
Call M-LINE at 800-962-3555 or visit mottchildren.org
Twelve years ago, graduate student Brian Zikmund-Fisher was forced into the toughest choice of his life: Die from a blood disorder within a few years or endure a bone marrow transplant that could cure him or kill him in weeks.

Zikmund-Fisher, now an assistant professor at the University of Michigan School of Public Health specializing in health communication, chose to gamble. After nine months of blood transfusions, a bone marrow match was found in Australia. Zikmund-Fisher spent another month in isolation until his new immune system began working.

“Unfortunately, today many patients don’t learn what they need to in order to make informed medical decisions.”

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“Unfortunately, today many patients don’t learn what they need to in order to make informed medical decisions.”

To document the challenges patients face in deciding their own medical care, Zikmund-Fisher, also an assistant professor in Internal Medicine at the U-M Health System, and Mick Couper, a research professor in survey methodology at the U-M Institute for Social Research, led a national survey of medical decisions featured recently in a themed issue of the journal Medical Decision Making.

The study surveyed more than 3,000 U.S. adults about nine common medical decisions. It was conducted by ISR’s Survey Research Center.

The conclusion: the majority of patients are unprepared to make the best decisions about medical care and need help from physicians even more than most physicians might suspect. For physicians, filling this need comes down to being an effective communicator, Zikmund-Fisher says.

“Be sure to check in with patients regarding what they want to do. Such explicit inquiries help patients to express their doubts or concerns and are a fundamental element of both informed and shared decision making,” he advises.

Zikmund-Fisher adds that physicians should tell patients pros and cons of treatments, something his research showed they don’t always do.

Physicians often have a lot of information to give to patients, but they need to keep it short by identifying key points, he says. “Focusing on a few critical details, like key side effects or expected duration of treatment, may be more valuable to patients than a flood of facts.”

Zikmund-Fisher also stressed that physicians shouldn’t overestimate a patient’s understanding of their own medical condition.

“We found that patients often don’t know as much as they think they do. So, don’t assume that a patient who seems confident about his or her knowledge is necessarily prepared to make an informed decision.”
NEW DISCOVERIES HINT AT POTENTIAL TARGETS FOR ASTHMA TREATMENT

Infections of white blood cells in asthmatic mice show an intense inflammatory response not seen in mice without asthma.

New laboratory-based discoveries by University of Michigan Health System researchers could explain why respiratory viruses like rhinovirus cause lower respiratory tract symptoms like coughing, chest tightness and wheezing in patients with asthma, but not in people without asthma.

In addition to providing a new framework to explain rhinovirus-induced asthma exacerbations, the work identifies new cellular and molecular targets for asthma therapy.

These findings appeared in the *Journal of Immunology* in late summer and are part of ongoing U-M research aimed at improving asthma treatment.

Viral infections are the most common cause of asthma flare-ups, and rhinovirus (a common cold virus) is the most common virus involved. Asthma exacerbations are the most common cause of children’s hospitalizations in the United States.

“This research will help us identify new cells and molecules for drug targeting,” Hershenson says. “There is currently no good treatment for virus-induced exacerbations.”

The research was led by Marc Hershenson, M.D., Frederick G.L. Huetwell Professor of Pediatrics and Communicable Diseases and professor of Molecular and Integrative Physiology.

Using mice and cell culture models, the team found that airway macrophages (white blood cells) from mice with allergic airway disease are polarized in such a way that, when infected with rhinovirus, they make proteins that attract inflammatory cells to the airway. Cells from normal mice do not respond to rhinovirus infection in this way. Elimination of the macrophages blocked the response to rhinovirus.

This study used a mouse model with human rhinovirus infection. It is the first study to show that rhinovirus infects inflammatory cells in addition to airway epithelial (lining) cells in animals or humans.

“This research will help us identify new cells and molecules for drug targeting,” Hershenson says. “There is currently no good treatment for virus-induced exacerbations.”

Understanding of the biochemical pathways responsible for rhinovirus-induced cytokine expression in airway macrophages could lead to new treatments for asthma, Hershenson says.

In another recent study, with results published in the October edition of the journal *Pediatrics*, Hershenson’s team showed that isolating a new type of cell, the mesenchymal stromal cell, predicts the development of a chronic lung disease in premature infants.

The article “Isolation of Tracheal Aspirate Mesenchymal Stromal Cells Predicts Bronchopulmonary Dysplasia,” concludes that the mesenchymal stromal cell may play an important role in the pathogenesis of chronic lung disease and could serve as a biomarker for adverse pulmonary outcomes in premature infants.

FOR MORE INFORMATION

Call M-LINE at 800-962-3555

Citation: *J. Immunology*, doi: 10.4049/jimmunol.1000286
SEPSIS SURVIVORS MORE THAN THREE TIMES AS LIKELY TO HAVE COGNITIVE ISSUES

Helping an older patient survive severe sepsis is a big hurdle for physicians. But a new study shows the road ahead doesn’t get smoother for these patients.

U-M research published recently in the Journal of the American Medical Association showed that 60 percent of hospitalizations for severe sepsis were associated with worsened cognitive and physical function among surviving older adults.

The odds of acquiring moderate to severe cognitive impairment were 3.3 times higher following an episode of sepsis than before, and much higher than for other general hospitalizations. Severe sepsis also was associated with greater risk for the development of new functional limitations following hospitalization, says lead author, Theodore (Jack) Iwashyna, M.D., Ph.D., assistant professor of internal medicine.

“We used to think of sepsis as just a medical emergency, an infection that you get sick with and then recover,” says Iwashyna. “But we discovered a significant number of people face years of problems afterwards.

Those problems are bigger and more common than we expected. Most older Americans suffer real brain and body problems after severe sepsis,” he continues. “We need new treatments, not just for the sepsis infection, but to prevent these new disabilities afterwards.”

Among patients who had no limitations before sepsis, more than 40 percent developed trouble with walking. Nearly one in five developed new problems with shopping or preparing a meal. Patients often developed new problems with basic hygiene functions.

“We need to make sure families have the resources they need to care for survivors of sepsis when they go home. It’s not enough just to get them through the acute episode. We need to start preparing them for the years of problems they may have afterwards,” says Iwashyna.

The research underscores the need for physicians who care for older adults to focus early on preventing infections that can lead to sepsis, says study co-author Kenneth M. Langa, M.D., Ph.D., a core investigator for the Ann Arbor Veterans Administration Health Services Research and Development Service’s Center of Excellence and professor of internal medicine at U-M.

“We need to make sure families have the resources they need to care for survivors of sepsis when they go home.”

Older patients need to get their flu and pneumonia vaccines in order to decrease their risk for infections, and physicians need to be aware of the long-term risk for cognitive and physical disabilities that many patients may face, Langa said.

“In contrast to Alzheimer’s disease and other forms of dementia, the cognitive impairment associated with sepsis is likely to be at least partially preventable through better acute care of the sepsis episode and better rehabilitation efforts afterwards,” Langa says.

FOR MORE INFORMATION

For more information about this trial contact Dr. Sara Saberi at 800-962-3555 or saberis@umich.edu.

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Hypertrophic cardiomyopathy (HCM) is a genetic heart condition that affects one in 500 individuals and is a major cause of sudden cardiac death in young people. Because the inherited thickening of the heart muscle is frequently asymptomatic, it can be a silent killer.

HCM can lead to chest pain that feels like angina and abnormal electrical heart rhythms that can result in passing out or, in tragic cases, sudden cardiac death. But proper care can give HCM patients a chance at better quality of life and peace of mind. Most treatments are aimed at relieving symptoms. Beyond medication, surgery can be an option.

“As one of only 19 hypertrophic cardiomyopathy programs in the country, we have learned a lot about this complex disease with its unique and challenging diagnostic and management issues,” says Sharlene Day, M.D., director of the Hypertrophic Cardiomyopathy Clinic.

“Through our work with genetic testing for these patients, we have discovered a need for expanding our practice beyond HCM to include other genetic cardiac disorders such as left ventricular noncompaction, arrhythmogenic right ventricular cardiomyopathy, dilated cardiomyopathies and other inherited cardiomyopathies” she says.

The HCM clinic is staffed by specialists in adult and pediatric cardiology, cardiac surgery and human genetics. Each patient undergoes initial consultation with a genetic counselor and cardiologist with coordinated non-invasive testing the same day. The majority of the patients will be seen by Day or two other physicians who specialize in echocardiography, Sara Saberi, M.D., or Renuka Jain, M.D.

Timothy Wilkes, 55, a runner from Dearborn, Mich., knew for 15 years that he had HCM, but it wasn’t until about five years ago that he started to experience symptoms.

“For a while there I wasn’t sure if I was just getting old or if it was part of the HCM. It turned out that it was mostly the HCM,” he says.

Wilkes had heart surgery at U-M in May 2009, and in October participated in his first road race in years.

The U-M is also participating in HCM research and has just begun enrolling patients in the first randomized exercise training study in HCM patients (see column opposite page). U-M is also a participating site for a multi-center study using genetics for early phenotyping and prevention of hypertrophic cardiomyopathy.

**FOR MORE INFORMATION**

Visit the Hypertrophic Cardiomyopathy Clinic website at [www.umcvc.org/hcm](http://www.umcvc.org/hcm)

To receive complimentary copies of the HCM patient brochure, please contact Erika Laszlo, the Cardiovascular Center Physician Liaison, at ellaszlo@umich.edu.

For Referring Physician Consult Guidelines on HCM, visit [www.med.umich.edu/umconsults](http://www.med.umich.edu/umconsults)
DRUG COMBINATION

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The study also included patients who were eligible for a stem cell transplant. The researchers found that these patients were able to remain on CRd treatment and achieved responses similar to or better than those observed after a stem cell transplant. This outcome delayed the need for a stem cell transplant in these patients.

“Newly diagnosed myeloma is most sensitive to treatment. A great response in the initial phase of treatment is critical because it projects how long patients will remain in remission, as well as their overall survival. Patients have a better chance of living longer if their response to initial treatment is better,” says Jakubowiak, who is an associate professor of internal medicine at the U-M Medical School.

Carfilzomib has recently emerged as an important drug in treatment of multiple myeloma. It has previously been tested as a single agent in patients who have exhausted all available treatment options and in relapsed disease. An ongoing Phase III trial is looking at CRd compared with lenalidomide and low dose dexamethasone alone for patients with relapsed multiple myeloma. Laboratory research suggests that carfilzomib works synergistically with lenalidomide and dexamethasone.

The Phase I study was conducted with funding from the Multiple Myeloma Research Foundation, Onyx Pharmaceuticals Inc., Celgene Corporation and the U-M Comprehensive Cancer Center. In addition to U-M, the multi-site study is being conducted at Mt. Sinai Medical Center, in New York; Hackensack University Medical Center, in New Jersey; Washington University School of Medicine, in St. Louis; and the Dana Farber Cancer Institute, in Boston.

The University of Michigan has a robust program in multiple myeloma research and was honored by the Multiple Myeloma Research Foundation as its 2010 Center of the Year. This is the second time U-M has received this award, which recognizes the efforts of an MMRC member institution in advancing the field of multiple myeloma research and drug development.

Jakubowiak, in particular, was recognized by MMRC for his strategic stewardship of pharmaceutical and biotech partners and for his leadership in catalyzing and advancing highly innovative pre-clinical and clinical research ideas. U-M currently has 14 clinical studies open testing new treatments for multiple myeloma.

About 20,000 Americans will be diagnosed with multiple myeloma this year, according to the American Cancer Society. “We are proud to be part of such a uniquely collaborative and highly respected model for accelerating the development of new treatment options for multiple myeloma patients and will continue to work urgently to bring patients the next generation of therapies,” Jakubowiak says.

FOR MORE INFORMATION

For more information about multiple myeloma research at U-M, call M-LINE at 800-962-3555 or visit UMClinicalStudies.org and search for study UMCC2010.040

Citation: http://ash.confex.com/ash/2010/webprogram/Paper28304.html