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Winter 2024/2025

Looking Toward the Future

MYELOMA CENTER CELEBRATES 35TH ANNIVERSARY

UAMS

from the director

Welcome to the latest issue of the *Myeloma* magazine as we celebrate 35 years of outstanding patient care and leading-edge research.

The Myeloma Center is a vital component of the exceptional treatment provided at the Winthrop P. Rockefeller Cancer Institute at the University of Arkansas for Medical Sciences (UAMS). Since my arrival in 2019, I have witnessed first-hand the remarkable dedication of the Myeloma Center faculty and staff under the leadership of Frits van Rhee, M.D., Ph.D.

"While we celebrate our past successes, we are looking towards the future."

Since the creation of the UAMS myeloma program in 1989, the management of this complex disease has progressed from standard chemotherapy to use of immunotherapies, which are easier to administer and less stressful on the patient. Many of these remedies are now available sooner after the initial myeloma diagnosis, which increases the chances of favorable results for the patient.

Translational research is a major factor in the march towards a cure for multiple myeloma. Fenghuang (Frank) Zhan, M.D., Ph.D., directs a superior program that is identifying new approaches in treating myeloma. The magazine details several sources of funding awarded to our research team, which allows us to continue on this path.

While we celebrate our past successes, we are looking towards the future. Novel therapies and advanced research are positive steps towards curing what was once thought to be a uncurable disease. This edition also contains inspirational patient stories as well as features on our superior health care professionals. Dr. van Rhee, the world's expert on Castleman disease, discusses UAMS' role in the treatment and understanding of this rare disease.

The UAMS Myeloma Center is the leader in myeloma care. We appreciate all who have put their trust in our team, and we will continue to do our best to deliver the care you need and deserve.

Michael Birrer, M.D., Ph.D.,
Vice Chancellor, University of Arkansas for Medical Sciences
Director, Winthrop P. Rockefeller Cancer Institute
Kent Westbrook, M.D., Director's Chair, Winthrop P. Rockefeller Cancer Institute

from the Myeloma Center Clinical Director

It is my great pleasure to present the Winter 2024/2025 issue of the *Myeloma* magazine. As we celebrate 35 years of myeloma care at the University of Arkansas for Medical Sciences (UAMS), we look forward to the future.

The increased use of novel immunotherapies, which are highly effective and less toxic, are a significant advancement in the treatment of multiple myeloma. UAMS is the only institution in the state of Arkansas authorized to use chimeric antigen receptor (CAR) T-cell therapy for myeloma. The CAR T-cell process is an infusion of the patient's enhanced immune cells designed to kill myeloma cells. Recent decisions by the Food and Drug Administration now allow the use of CAR T-cell therapy earlier in the regimen at first relapse. We believe this will help patients by giving them access to this therapy closer to the beginning of their initial myeloma diagnosis and will improve outcomes. UAMS is also taking part in an exciting large international trial in which CAR T-cell therapy is used to treat patients with newly diagnosed myeloma. The trial aims to answer the important question as to which is better: standard autologous stem cell transplant or CAR T-cell therapy?

Bispecific antibodies are also a new therapy that activates the patient's immune cells to kill myeloma. No complex manufacturing process is needed, and a major advantage is that these antibodies are ready to use off-the-shelf. The Myeloma Center is planning a clinical trial for patients with newly diagnosed high-risk myeloma. Two of these antibodies, each aiming at a different target on myeloma cells, will be incorporated in the front-line therapy. We hope that this innovative approach will improve the outcome of these patients.

Minimal residual disease (MRD) tests on bone marrow are used to detect small amounts of myeloma, even when bone marrow looks normal upon initial examination. We have routinely been testing patients for MRD since 2013. We are studying whether therapy can be discontinued early when patients have several negative tests. We are also testing whether therapy should be optimized for those with high-risk disease who have a positive MRD.

I hope that you enjoy reading about the experiences our patients have had at UAMS. The magazine contains features on members of our staff, details on clinical trials and research efforts led by Fenghuang (Frank) Zhan, M.D., Ph.D., who directs our translational research team.

We continue to advocate that myeloma is curable, and many of our patients have excellent long-term outcomes without relapse. These treatment advancements and the more individualized approach to therapy offer hope to patients and to all who are involved in patient care.

Frits van Rhee, M.D., Ph.D. MRCP(UK) FRCPath
Clinical Director of the Myeloma Center
Charles and Clydene Scharlau Chair for Hematologic Malignancies Research

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UAMS myeloma

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EDITOR
Nathan Tidwell

CREATIVE DIRECTOR
Mindy Stout

PHOTOGRAPHERS
Bryan Clifton
Evan Lewis

DIRECTOR
UAMS Winthrop P. Rockefeller Cancer Institute
Michael Birrer, M.D., Ph.D.

CLINICAL DIRECTOR
Myeloma Center
Frits van Rhee, M.D., Ph.D.

DIRECTOR OF RESEARCH
Myeloma Center
Fenghuang (Frank) Zhan, M.D., Ph.D.

CHANCELLOR
University of Arkansas for Medical Sciences
Cam Patterson, M.D., MBA

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4301 W. Markham St. #816
Little Rock, AR 72205

Phone: 501-526-2873
myeloma.uams.edu

Looking Toward the Future

Myeloma Center Celebrates 35th Anniversary

The Myeloma Center, located in the Winthrop P. Rockefeller Cancer Institute at the University of Arkansas for Medical Sciences (UAMS), has firmly established itself as an international leader in myeloma treatment. From its beginnings in 1989, UAMS' myeloma program is recognized for detailed patient care, groundbreaking research and pioneering advances in the management of myeloma and its related conditions.

From the Total Therapy approach, the introduction of tandem autologous transplants, the creation of a prediction model for stem cell collection and the current implementation of innovative immunotherapies, the path towards a cure for myeloma continues — with UAMS leading the way.

Myeloma Center Clinical Director Frits van Rhee, M.D., Ph.D., and his team embrace the task of developing new methods of treating this disease.

"Patients and providers worldwide know the UAMS Myeloma Center and the Winthrop P. Rockefeller Cancer Institute as the best option to receive care for this condition," said Cam Patterson, M.D., MBA, UAMS chancellor and CEO of UAMS Health. "The standard of excellence by this dedicated group of health care professionals is unmatched, and we look forward to a brighter future in the course of myeloma research and treatment."

The Process

The exact cause of myeloma is unknown, which presents unique challenges for physicians and researchers. Many of the symptoms are common to other conditions, and symptoms may not present themselves in the disease's early stages. Total Therapy, pioneered at UAMS, was a revolution in myeloma treatment.

"This approach uses induction chemotherapy to bring the disease under control," van Rhee said. "Autologous stem cell transplants are followed by consolidation treatment to further reduce the cancer. Maintenance therapy is used to prevent relapse."

Patients typically receive three drugs (dexamethasone, Revlimid and Velcade) for three years. Approximately 30% of patients who have a

Our clinicians

Frits van Rhee, M.D., Ph.D.

Samer Al Hadidi, M.D.

Carolina Schinke, M.D.

Sharmilan Thanendrarajan, M.D., Ph.D.

Maurizio Zangari, M.D.

standard risk of myeloma will not relapse. The anti-CD38 monoclonal Darzalex was introduced, which further enhanced the efficiency of this approach.

Van Rhee notes two main challenges in treating myeloma.

"Not all patients are fit enough to receive such a comprehensive treatment approach. Also, the cure rate of more aggressive myeloma is much lower."

The need for more effective and less toxic therapy led the Myeloma Center into the next stages of myeloma treatment.

Bispecific Antibodies

The advent of bispecific antibodies plays a crucial role in myeloma treatment, particularly for those patients with relapsed refractory myeloma. Bispecific antibodies are constructed to bind to both myeloma cells and immune cells, which activates T-cells to destroy cancer cells.

"Bispecific antibodies have been a game-changer," said Myeloma Center physician and researcher Carolina Schinke, M.D. "They're very effective. They have toxicities, but we're learning how to treat them."

The following treatments have been approved by the Food and Drug Administration (FDA) for use with myeloma patients:

- Elranatamab
- Talquetamab
- Teclistamab

"Clinical trials for bispecific antibodies are ongoing for treatment in the earlier stages of myeloma," van Rhee said. "One trial is with the bispecific antibodies talquetamab and teclistamab as a front-line treatment for high-risk myeloma."

An important benefit of antibody therapy is it is immediately available for injection and does

1989

The Myeloma Center, then the Myeloma Institute, **introduced** tandem transplant approach.

1991

Ken Stoll became the **first** patient in the world to receive a stem-cell transplant on an outpatient basis.

not require chemotherapy. Bispecific antibodies may also be a preferred option for patients who cannot tolerate standard chemotherapy.

"We hope that this innovative therapeutic approach will improve outcomes for high-risk patients," said van Rhee.

CAR T-cell Therapy

Chimeric antigen receptor (CAR) T-cell therapy is a revolutionary option for patients who have had several lines of treatment. Already in use with other forms of cancer, in 2021 the Myeloma Center performed this procedure on a myeloma patient for the first time in Arkansas. UAMS is the only medical facility in the state where this therapy is available for those diagnosed with myeloma.

"CAR T-cell therapy has greatly improved the treatment of patients with relapsed myeloma," said van Rhee.

CAR T-cell is B-cell Maturation Antigen (BCMA) targeted therapy, in which the patient's T-lymphocytes immune cells are collected and manufactured to recognize the BCMA protein on the surface of myeloma cells. After infusion, the manufactured CAR T-cells activate and destroy myeloma cells.

"One advantage of CAR T-cell therapy is that it's a very personalized approach," said Syed Naqvi, M.D., a Myeloma Center hospitalist who performs this procedure. "By using the patient's own cells, they can be engineered to fight the disease specifically in that patient."

The FDA approved ide-cell (idecabtagene vicleucel, ABECMA) in March 2021 as the first CAR T-cell

1997

Introduced thalidomide as a treatment for multiple myeloma.

1998

First to utilize PET scan for diagnosis and assessment of treatment response.

product for myeloma patients who had received at least four different treatments. Clita-cel (ciltacabtagene autoleucel, CARVYKTI) received FDA approval in February 2022 for patients with minimal or no response to previous treatments, or for those who have relapsed after four lines of therapy.

In April 2024,, the FDA approved the use of these therapies earlier in the treatment process. Ide-cell may now be administered to patients with relapsed refractory myeloma who have had at least two prior lines of treatment. Clita-cel is now available for those who have received at least one prior line of therapy.

"We have treated almost 100 patients with CAR T-cells and are very excited about the results," van Rhee said.

"The future of CAR T-cell therapy is very promising," Naqvi said. "If we're able to treat patients earlier, those patients may have healthier cells, and we may be able to achieve better results as opposed to patients who have had multiple lines of treatment."

Patient Care

Patient care is the top priority for the Myeloma Center team.

The complete array of services available dramatically shortens the time patients are required to be at UAMS for appointments. Blood work, MRIs and positron emission tomography (PET) scans are all offered on-site, with results promptly available for review by the patient and physician.

"We have a tremendous advantage here because the patient doesn't have to go anywhere else for tests," said van Rhee.

2006

Identified seven molecular genetic subtypes of myeloma and their bearing on prognosis.

2007

First to use gene expression profiling for risk stratification and assignment to therapy.

This is especially important for the many out-of-state patients who receive treatment at the Myeloma Center. A patient can complete all requested tests one day, then visit with their physician and leave the following day.

The advent of novel therapies allows the Myeloma Center to further its goal of personalized treatment for each patient, based on factors such as age, overall health, laboratory and imaging results, and any prior treatment.

"Not all methods work for all patients," van Rhee said. "Tailoring the plan for each person allows us to specifically target the myeloma and provide the best chance of cure with minimal side effects."

Going Forward

The next phase of myeloma care includes further movement away from traditional chemotherapy and more use of immunotherapies, van Rhee said.

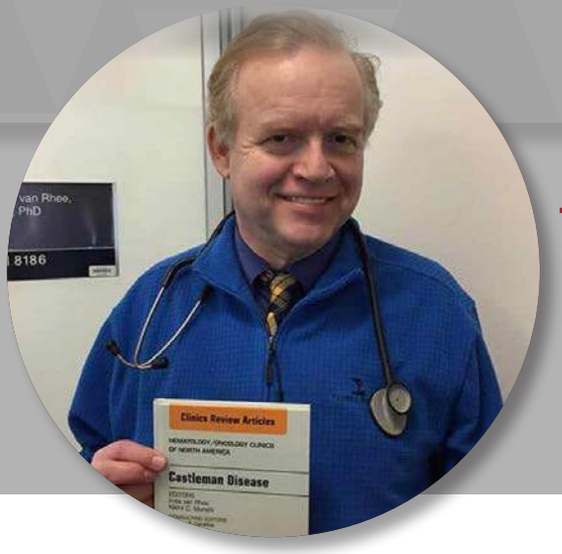
"An important question is whether CAR T-cell therapy can replace autologous stem cell transplants," he said. "The Myeloma Center is participating in a large international trial where patients are being randomly allocated to either CAR T-cell therapy or stem cell transplants in hopes of answering this question."

Immunomodulatory drugs such as Revlimid and thalidomide modify or regulate the immune system. Proteasome inhibitors, which include Ninlaro and Velcade, target

2014

10+ year follow-up indicates that **cure is achievable** for patients with low-risk myeloma.

2018



First book on Castleman disease is published.

enzymes that remove waste proteins from cells and keep them healthy. Monoclonal antibodies such as Darzalex target specific proteins on myeloma cells.

The Myeloma Center is authorized to perform CAR T-cell therapy as an outpatient procedure, which is another benefit for patients who are healthy enough to recover at home.

Still, there are significant questions remaining to be answered regarding the future of myeloma treatment, van Rhee said.

"Both CAR T-cell therapy and bispecific antibodies have unique side effects. Individual patient selection for the most appropriate therapy is important. It is also crucial to understand why some patients relapse after these therapies.

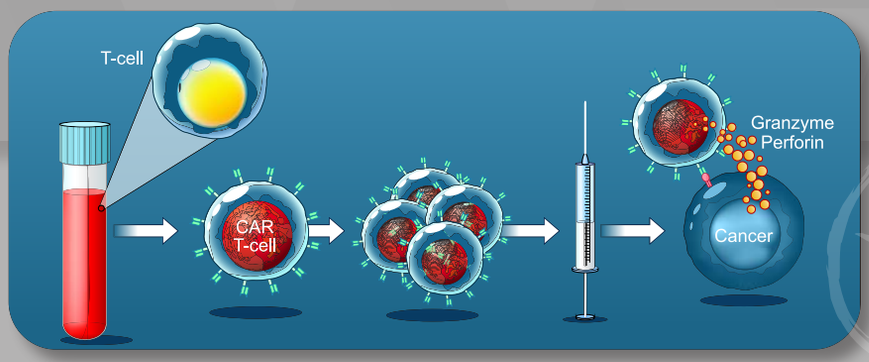
"Novel approaches and new drugs are being developed, which will hopefully still further improve outcomes," he continued. "One class of drugs are referred to cereblon E3 ligase modulators (CELMoDs), which are more effective versions of the immunomodulatory drugs lenalidomide and pomalidomide. New generations of CAR T cells and bispecific antibodies are also being developed."

"A lot of research is happening to determine how to best combine all of these new treatment options," van Rhee said. "Overall, these are very exciting times, and we hope to make even more progress in the coming years."

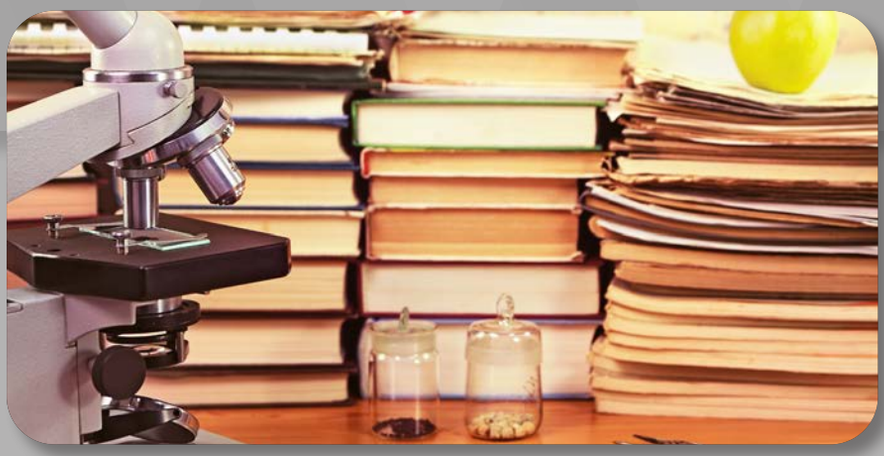
"An important question is whether CAR T-cell therapy can replace autologous stem cell transplants."

2021

Performed Arkansas' **first** chimeric antigen receptor (CAR) T-cell therapy treatment for myeloma.

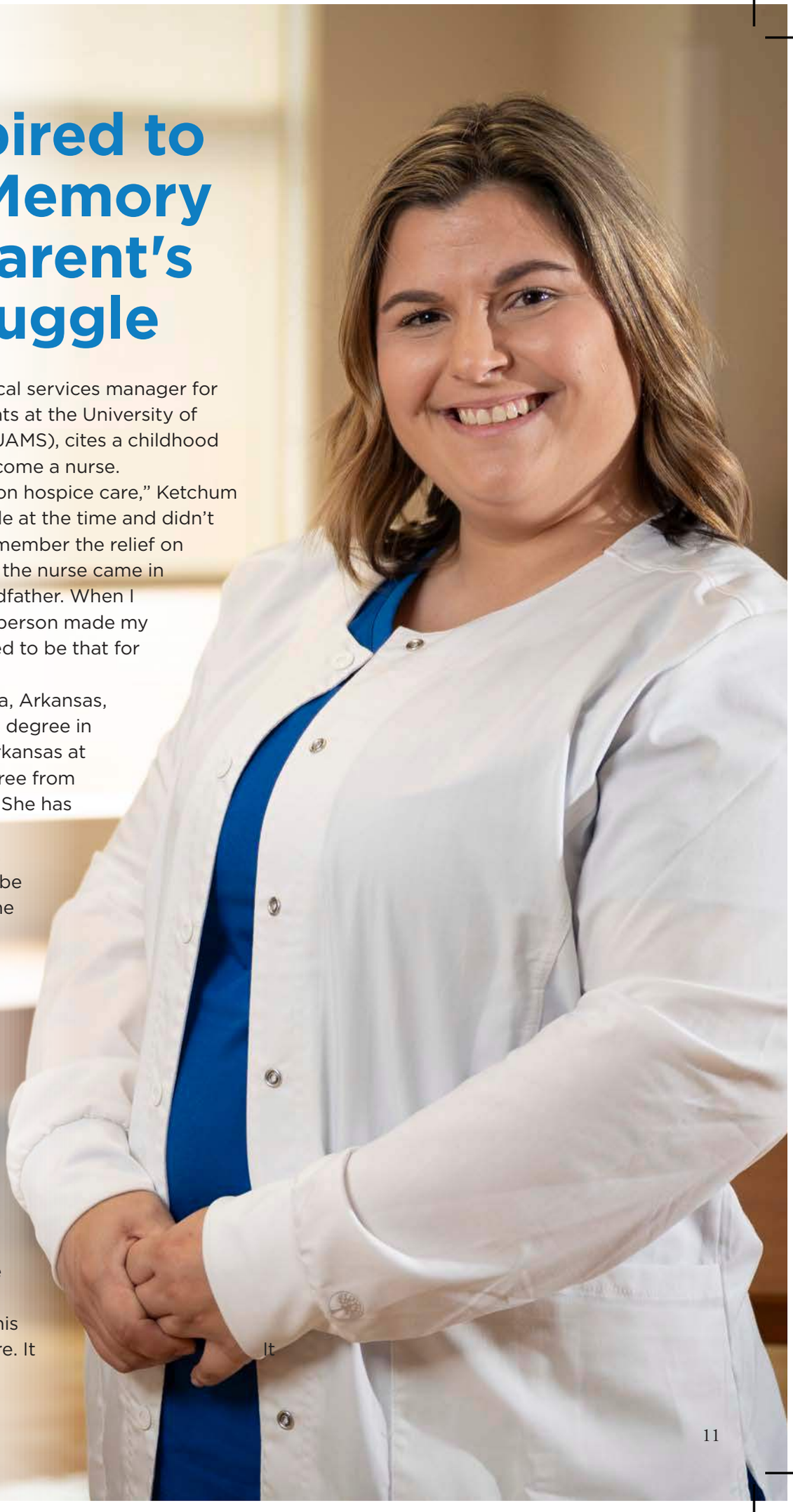


2023



Published **1,000th** research paper.

Nurse Inspired to Serve by Memory of Grandparent's Health Struggle



Christina Ketchum, MSN, clinical services manager for myeloma stem cell transplants at the University of Arkansas for Medical Sciences (UAMS), cites a childhood memory as her inspiration to become a nurse.

"My grandfather was at home on hospice care," Ketchum said. "I was in fourth or fifth grade at the time and didn't fully understand everything. I remember the relief on my grandmother's face any time the nurse came in to help her take care of my grandfather. When I got older and recalled how that person made my grandmother feel, I knew I wanted to be that for someone."

A native of Helena-West Helena, Arkansas, Ketchum received her bachelor's degree in nursing from the University of Arkansas at Little Rock and her master's degree from Benedictine University in Illinois. She has been at UAMS since 2014.

Ketchum explained the various scenarios where a patient might be admitted to hospital as part of the stem cell transplant process.

"Some may be a direct admission prior to the planned treatment. A patient may be newly diagnosed with myeloma and need a workup," she said. "We also get patients who may have started their treatment as an outpatient but now need 24-hour care."

Ketchum expressed her gratitude for her UAMS team and the patients they serve.

"Even on the hard days, I come back for the patients and the people I work for. I grew up on this floor — I was 23 when I came here. It really feels like a family."

Myeloma Center Focuses on Immunotherapy Drugs in Latest Clinical Trials

Samer Al Hadidi, M.D.

Carolina Schinke, M.D.

Multiple myeloma treatment is advancing with the advent of bispecific antibody drugs, which use the patient's T cells to fight the disease. Myeloma Center physicians and researchers Carolina Schinke, M.D., and Samer Al Hadidi, M.D., are leading clinical trials exploring combinations of these novel therapies.

Schinke's trial is studying the effects of using teclistamab and talquetamab in combination. Al Hadidi's trial looks at daratumumab, Revlimid and Velcade used with dexamethasone, a steroid.

"Current FDA approval is for either talquetamab and teclistamab," said Schinke. "Both have excellent and unprecedented results for those with relapsed refractory myeloma. The only patient population that does not respond well to either of these drugs are those with extramedullary disease, where the myeloma has progressed out of the bone marrow to other organs.

"In this trial we're combining both of these drugs to see if the combination is more successful in treating patients with extramedullary disease. Myeloma has been historically difficult to treat once it is outside of the bone marrow," Schinke added.

Al Hadidi is working with three combinations of drugs for newly diagnosed multiple myeloma patients who may need a different treatment plan than typically prescribed.

"These regimens are for patients where stem cell transplants may not be viable," Al Hadidi said. "These patients are older or frailer, and previously they had fewer options."

> "These regimens are for patients where stem cell transplants may not be viable."

One treatment Al Hadidi is studying uses RVd (Revlimid, Velcade, dexamethasone). Two of the potential treatments use a combination of daratumumab, Revlimid and dexamethasone, with the difference being the patient receiving only Revlimid in the maintenance phase in one and daratumumab and Revlimid in the other.

"We're trying see if one of the three protocols will be better at controlling the disease and reducing side effects," said Al Hadidi.

Clinical trials are a vital part of research, and the Myeloma Center continues to be a leader in multiple myeloma treatment.

Funding Awards Amplify Myeloma Research

Fenghuang (Frank) Zhan, M.D., Ph.D.

At the UAMS Myeloma Center, Fenghuang (Frank) Zhan, M.D., Ph.D., knows that research plays an immensely important role in the fight against multiple myeloma. Numerous federal grants allow the center's director of research and his team to continue to advance and improve treatments, benefitting myeloma patients around the world.

The latest is a $1.1 million award from the U.S. Department of Veterans Affairs (VA-Merit) to study drug resistance in multiple myeloma.

"Drug-resistant tumor cells are the most probable source of relapsed refractory multiple myeloma. Our aim is to identify biomarkers of drug-resistant multiple myeloma cells and develop novel targeted therapies aimed at eliminating those cells," said Zhan. "This will provide new insights into how drug-resistant multiple myeloma cells can influence cancer cell behavior and allow us to create immunotherapies to prevent relapse."

Additionally, Zhan received $750,000 from the Leukemia & Lymphoma Society in July to research improvements in chimeric antigen receptor (CAR) T-cell therapy. Earlier, he received $500,000 from the Myeloma Solution Fund in March to develop novel therapy targeting myeloma patients with chromosomal t(4;14).

In September 2023, Zhan and John D. Shaughnessy Jr., Ph.D., professor of medicine, also received a $1.78 million U54 grant from the National Institutes of Health (NIH).

This funding is towards a study on monoclonal gammopathy of undetermined significance (MGUS), a premalignant condition of antibody-producing plasma cells that can frequently progress to multiple myeloma or Waldenstrom's macroglobulinemia.

"The long-term objective is to determine the functional role of the bone marrow microenvironment in the development of MGUS and its eventual progression to myeloma," Zhan said.

Shaughnessy directs the bioinformatics core of the NIH project.

"Our goal is to provide in-depth molecular analysis of malignant plasma cells and the cells of the bone microenvironment isolated from patients enrolled in clinical trials over the past 25 years at UAMS, with the aim of distinguishing targetable molecular events in MGUS that progressed to multiple myeloma or Waldenstrom's macroglobulinemia that has remained stable," said Shaughnessy.

Additionally, Zhan's lab is working with grants from the NIH R01 and the Riney Foundation totaling nearly $5.6 million. This research focuses on NEK2 genes and how they signal myeloma. The goal is to use new technology to develop CAR T cells or antibodies to target certain types of myeloma and attack tumor cells while preserving normal cells.

"Drug-resistant tumor cells are the most probable source of relapsed refractory multiple myeloma."

Myeloma Center Physician Driven by Desire to Help Patients

In his 11th year with the Myeloma Center at the University of Arkansas for Medical Sciences (UAMS), Sharmilan Thanendrarajan, M.D., Ph.D., knew he wanted to be a physician at a young age.

"When I was in high school, I liked biology, chemistry and physics and decided to go in that direction," said Thanendrarajan, an associate professor of medicine who is known affectionately as "Dr. T" by colleagues and patients. "The desire to help people was a driving force."

"I had this very sick multiple myeloma patient with only limited treatment options, and I had a strong desire to learn more about how to help."

Thanendrarajan earned his medical degree and doctorate in medicine from the Medical College of Ruhr-University in Bochum, Germany. He completed his fellowship in hematology and oncology at the University Hospital Bonn in Bonn, Germany, and his residency in internal medicine at the University Hospital Bonn and the General Hospital Hagen in Hagen, Germany.

A patient of his in Germany prompted an interest in myeloma.

"I had this very sick multiple myeloma patient with only limited treatment options, and I had a strong desire to learn more about how to help. I was looking for the best place in the world to treat and research multiple myeloma, and all the leading myeloma experts in Germany told me to go to the UAMS Myeloma Center in Little Rock, Arkansas."

"We apply a customized plan for each patient, taking into account the patient's fitness and comorbidities, as well as biology and genetics of the cancer. At UAMS we do the most detailed and comprehensive diagnostics, using latest technologies — blood, urine,

Thanendrarajan and Anne Williams, APRN, visit with patient John Lafave.

bone marrow tests and imaging studies. We get a 360-degree view of the patient and work together as a team to come up with a strategy and plan."

Thanendrarajan expressed optimism about the future of myeloma treatment. "This has been the best time ever for multiple myeloma patients. "Thanks to the available novel immunotherapeutic approaches, including bispecific antibodies and CAR T-cell therapy, we're able to bring more patients into cure and improve overall survival rates."

Jeff Williams with his wife, Leigh Ann.

24-Year Myeloma Survivor Cites Positive Attitude as Key to Longevity

"Get as much exercise as possible."

Jeff Williams maintains a basic approach to living with multiple myeloma.

"Get as much exercise as possible," he said. "I work about a mile from a YMCA. I stay in shape. It has to be a habit. If you go long enough, it will become a habit. Resistance training builds bone density."

Williams, 66, is a native of Selma, Alabama, and currently lives in Hoover. He has worked in sales for Southland Pipe and Supply in Bessemer since 1998.

"I probably have about three or four years there before retirement," he joked.

Williams credits his employer, family and friends with helping him through this process.

"Southland Pipe has been great, particularly in the early years of treatment. I would be out for transplants for three to

four weeks each time in those days, and they'd tell me to come to work when I was feeling better," he said.

"My family and friends did everything," Williams continued. "Cooked meals, dispatched kids to practices. They were there with me during the tough times. After 24 years they still ask how I'm doing."

Williams' path to learning he had multiple myeloma is a familiar one — it began with an injury.

"I played church league softball and volleyball for years. My right rib cage was hurting for about a year."

He received his diagnosis in March 2000.

"Hearing that I had multiple myeloma scared me to death. I had never heard of it before, but I learned quickly. I had a test that week, but my local internist didn't tell me until Monday morning — he said he didn't want to ruin my weekend. That day I had a biopsy on my rib and the results revealed plasmacytoma."

Williams shared his initial feelings about being recommended to come to UAMS.

"A day later I met with my local oncologist and had my first bone marrow biopsy. He told me he was sending me to Little Rock for treatment. I looked at him like he was crazy. I asked, 'Why Little Rock?' He asked me how many I children I had, and I said three. He said, 'You have no choice.' I've been onboard ever since."

"I had never been to Little Rock before. The Myeloma Center looks nothing like it did in April 2000. I had all the blood work, tests and scans done. I met Dr. Maurizio Zangari and signed on with the Total Therapy 2 study. I had a game plan. I kept everything positive and attacked it."

Williams had his first stem cell transplant in July 2000, followed by another one that November.

Jeff Williams continues to lead a normal life despite his myeloma diagnosis.

"I was in remission during the induction phase before my first stem cell transplant. I was also allowed to do the transplant phase on an outpatient basis. The transplant phase is a lot to deal with. It's hard not only on the patient but your caregiver as well."

Despite his condition, Williams does not let it him hold him back.

"I live a very normal life," he said. "In 2007 I asked my oncologist if I could train and run a half marathon. During training, I was able to raise a little more than $5,000 for the Leukemia & Lymphoma Society through Team In Training. I ran the Country Music Half Marathon in Nashville — I didn't win it, but I did finish. It was a great experience and I'm thankful to have had the opportunity to do it."

Williams praised the treatment he's received at UAMS.

"I love Dr. Zangari to death. He's very thorough," he said. "He's very nice, comical in a lot of ways. We keep it light. When it comes to business, he tells it like it is."

He added, "I'm the beneficiary of a lot of research and science over the last 24 years. When I started, a lot of the drugs in use now weren't available. Now they have the treatment fine-tuned — it's fascinating."

His current protocol includes a Zometa infusion four times a year with a local oncologist, in addition to taking Ninlaro. He visits UAMS once a year to meet with Zangari.

"The people at UAMS are very efficient. Everyone there is a professional — I've had nothing but good experiences," said Williams.

Williams offers these thoughts to others with the disease.

"Listen to your body. When my friends complain about pain and illness, I tell them to go to a doctor. In my case, I waited way too long to go. The main thing I stress is to not let yourself get down. Have the attitude that you're going to whip this thing."

70 Years after Discovery, UAMS Myeloma Center, Castleman Disease Collaborative Network Lead the Way in Understanding Disease

By Frits van Rhee, M.D., Ph.D.

Castleman disease was first described in 1954 by Benjamin Castleman, M.D., longtime chief of the Division of Anatomic Pathology at Massachusetts General Hospital in Boston. Patients with Castleman disease have enlargement of one or more lymph node areas.

Frits van Rhee, M.D., Ph.D.

Patients who have the disease in one area, unicentric Castleman disease, can be effectively treated by surgery. Those with enlargement of multiple areas have flu-like symptoms such as fatigue, fever, loss of appetite and weight loss. This is referred to as multicentric Castleman disease. In severe cases, these patients can develop kidney and other organ failures or may even succumb to the disease. In some cases, especially with HIV patients, the disease is caused by a virus called human herpesvirus type 8. However, in many cases the cause is unknown, and in these cases the disease is referred to idiopathic multicentric Castleman disease (iMCD).

Researchers in Japan showed in the early 1990s that a cytokine called interleukin 6 (IL6) was in many cases responsible for the clinical symptoms and lymph node enlargement in iMCD. In 1994, the Myeloma Center treated the first patient with a monoclonal antibody targeting IL6, a seminal finding that was published that year in the *New England Journal of Medicine*. This study proved proof of principle that targeting IL6 was a valid therapeutic approach. However, the first antibody proved difficult to administer and the effects were temporary. Researchers in the Netherlands developed an improved antibody, now known as siltuximab, that neutralizes IL6 in the peripheral blood.

The initial results in a dose finding Phase 1 study were positive and followed by a large international study, the first ever in Castleman disease, conducted in Brazil, Canada, New Zealand, Australia, Egypt, Taiwan, Hong Kong, Singapore and the United States, as well as in Europe. As a result, siltuximab became the first treatment for Castleman disease approved by the Food and Drug Administration (FDA). UAMS played a leading role in these studies on which I was the principal investigator.

However, not all patients responded to siltuximab, and the cause of the disease was still elusive. A patient of mine, medical student David Fajgenbaum, and I founded the Castleman Disease Collaborative Network (CDCN) in 2015. Fajgenbaum, now a physician-scientist at the University of Pennsylvania and the co-founder and president of Every Cure,

"UAMS and the Myeloma Center are extremely focused on the patient experience," said David Fajgenbaum, M.D., who was a medical student when he met his physician Frits van Rhee, M.D., Ph.D., but today collaborates with him on several projects related to Castleman disease.

details his personal journey in his book, "Chasing My Cure."

The CDCN is a worldwide network of researchers and physicians who collaborate to advance our understanding of Castleman disease. Patient advocacy is an important component of the CDCN, which aims to facilitate patient education and provides a portal for patients to connect with Castleman disease experts. Patients can further participate by submitting their medical record data to CDCN's ACCELERATE registry, established to develop a better picture of the natural history of the disease. This has already led to a better understanding and classification of the disease. Patients and their doctors can further help by submitting blood and lymph node samples to a large biorepository (CastleBank), which is utilized for research studies funded by the CDCN. Protein studies done on the peripheral blood have identified biomarkers that are predictive of response to siltuximab.

The CDCN developed the first international consensus diagnostic criteria for iMCD to accurately define the disease and to distinguish it from other disorders that give rise to similar clinical and lymph node findings. Historically, as many as one-third of patients died from iMCD, partly because there was no uniform approach to treatment based on sound clinical evidence. That lack of guidance resulted in a wide variety of treatments being used to manage the condition. The CDCN's treatment guidelines recommend drugs such as siltuximab as first-line therapy.

Because not all patients respond to siltuximab, the search for additional treatments continues. Detailed studies have shown that some patients may benefit from sirolimus, an immunosuppressive drug that is used to prevent organ rejection after a kidney transplant. More recently, laboratory studies guided by the CDCN have discovered that some patients may benefit from targeting IL6 in a different way. A new clinical trial is being developed by the CDCN with a class of drugs that targets IL6 signaling inside the cell.

Overall, our understanding of Castleman disease has greatly improved since the disease was first identified in 1954.

We have improved the classification of Castleman disease and developed both diagnostic criteria and a therapeutic algorithm. We now have an FDA-approved drug available for iMCD. Research has also uncovered potential novel drugs for siltuximab non-responders. The cause of iMCD has remained elusive, but a viral cause has been confidently excluded. Detailed single cell sequencing studies and other state-of-the-art analyses of lymph nodes are in progress, which hopefully will shed further light on this complex and enigmatic disorder.

Juan Carlos Rico, M.D., and Melissa Standridge, RN, review schedules.

Partners *in* Care

Prevention is the Key for Keeping Infectious Diseases at Bay

Myeloma patients face several issues, one being compromised immune systems that make them more prone to infection. The UAMS Division of Infectious Diseases plays an important role in ensuring patients are in the best position to continue their cancer treatment.

Under the direction of Michael Saccente, M.D., the Division of Infectious Diseases is part of the UAMS College of Medicine's Department of Internal Medicine.

"We help with preventing infections and help treat infections when they occur," said Juan Carlos Rico, M.D., an associate professor who has been with the division since 2014. "We try to come up with guidelines to prevent infections and help patients during their cancer treatments."

"It takes a lot of time and effort, particularly with myeloma patients," said Michael Lowry, M.D., an assistant professor who has been with UAMS since 2021 and is a 2014 graduate of the UAMS College of Medicine. "Myeloma is disease that presents unique complications."

Infectious diseases are illnesses caused by such pathogens as bacteria, fungi, parasites and viruses. Those with underlying medical conditions such as diabetes or heart or kidney disease are more likely to acquire infections. Patients undergoing procedures requiring urinary catheters or other tubes are also more at risk.

For myeloma patients, chemotherapy, immunotherapy and stem cell transplants severely weaken the immune system. To better protect patients from infections, the medical team needs a heightened awareness, including knowing what treatments the patient is undergoing.

"We work with the oncologists to ensure the patient is able to go through treatment," Rico said. "We also review all of a patient's past therapies for previous complications or infections.

"It matters if a patient has never had chemotherapy, or if they're in the hospital after getting a stem cell transplant and they need maintenance chemotherapy. There could be totally different side effects," Rico continued.

Patients may be unaware of past infections, making the team's involvement even more important.

"If a patient has had previous infections, it's possible the infection can come back," said Rico. "We'll discuss and recommend a plan for prevention."

"Any type of minor infection can be life-threatening," said Lowry. "If there's any concern at all, they want to get us involved to prevent bad outcomes."

Lowry noted that sometimes no action is better.

"It's also important to know when not to treat something," he said. "It may be a case where the issue will resolve itself or addressing it may interfere with myeloma treatment."

The Infectious Diseases team intervenes in a variety of situations, Lowry said.

"The most common call we receive is about a patient who has had recent chemotherapy, and they have a fever for some unclear reason," he said. "Sometimes we get confusing clinical pictures. It's like detective work — putting the pieces together."

Communication is a key part of this process.

"A patient may have an abnormal lab or abnormal imaging on a PET scan," said Rico. "A nurse will send cultures, and if anything is positive, we will be contacted. We follow up with them as an outpatient and remain in contact to ensure the problem doesn't return."

"We work closely with the myeloma physicians, nurses, clinic staff, the hospitalists as well as the Infusion Center," Lowry said. "We want to present a united front with the patient so they don't feel in the dark about what's going on."

Lowry enjoys working with the Myeloma Center.

"A great thing about working with myeloma patients is you may see someone from down the street or someone from across the country. I want to continue our reputation as the best center in the world."

Rico summarized the goal of his division.

"Prevention is the key. If we can prevent a patient from having infections, it's the best thing."

our infectious diseases team

Mitchell Jenkins, M.D.

Michael Lowry, M.D.

Juan Carlos Rico, M.D.

"Sometimes we get confusing clinical pictures. It's like detective work -- putting the pieces together."

Myeloma Warrior Offers Support to Others in Fight

Alan Stephenson has taken his myeloma diagnosis and turned it into a positive for himself and others in this situation.

"One of the reasons I'm passionate about being an advocate is to let people know what to expect. The fear of the unknown is often a lot more than what you actually face," he said.

A financial advisor who lives near West Monroe, Louisiana, Stephenson is the creator of the Facebook support group, "Multiple Myeloma Warrior Community."

"I want it to be a place where all people can come together and love and support each other, along with sharing knowledge about this illness," Stephenson said.

The group has grown to more than 8,900 members since its creation in March 2023.

"I thought it would take a year to get 1,000 members," he said.

Stephenson's path to advocacy began with his own diagnosis.

"I had been in pain for a long time, but I thought it was old injuries coming back to haunt to me because I was hard on my body when I was younger. One day during the summer of 2015 I sneezed, and it put me on the floor. I injured my back, and I thought I had fractured a rib, but I didn't go to a doctor," he said.

"In March 2016 I was home alone, but I was sick," he continued. "I got in the shower, started coughing, and I went down. After a few minutes I was able to stand up, get dressed, drag myself to my truck and go to work."

That episode finally prompted Stephenson to seek help.

"The next day I saw my primary care physician. I had two MRIs scheduled, and I asked what the chances were that I had bone cancer."

The MRIs revealed a finding of multiple myeloma, along with a collapsed vertebra.

"When I was told it was multiple myeloma, they said go to the University of Arkansas for Medical Sciences [UAMS] — it's the best place in the world," said Stephenson. "I'd never heard of multiple myeloma. I thought it was no big deal because it wasn't brain or pancreatic cancer. I came to UAMS and found out I was wrong."

Stephenson describes his feelings when arriving at the UAMS Winthrop P. Rockefeller Cancer Institute.

"When they called me and asked to me come, I said OK and hung up. I didn't ask them anything. My wife was very upset with me," he said. "When we got there, we were terrified because we didn't know what to expect."

Myeloma Center clinical director Frits van Rhee, M.D., Ph.D., is Stephenson's physician.

"I love Dr. van Rhee," Stephenson said. "Everyone I've dealt with at UAMS – from the doctors to the people working in the pharmacy to the people who clean — are very friendly and supportive. One of the best things about UAMS are the volunteers who help the new patients. We had a volunteer who took my wife and I around the hospital when we got there, and it was a blessing."

Stephenson's current treatment includes meeting with a local oncologist every four to six weeks along with quarterly visits to UAMS.

"UAMS does more testing than anyone I've seen — they keep a close eye on their patients," he said.

Throughout his cancer journey, Stephenson says he has been searching for a community of myeloma survivors that supports each other. Eventually, he decided to create it himself.

"Patient advocacy has always been a big thing for me. I saw one decent-sized myeloma group online, and it was very depressing," he said. "It seemed like nothing but bad news, and if anything about prayer or spirituality was mentioned you were kicked out. I believe for a lot of people that's a very important thing."

His family is concerned about how much administering the support group takes out of him.

"My wife wondered whether being involved with the group would get to me, and sometimes I have to step away for a couple of days and take a break," said Stephenson.

Ultimately, Stephenson says he gets as much from the group as he gives to it.

"One message I try to give people is everyone is going to go through some sort of difficult situation in their lifetime. We can either be victims or victors over our circumstances — it's our choice. The people who love us are watching to see how we react. We set the example."

"One of the reasons I'm passionate about being an advocate is to let people know what to expect."

MYELOMA CENTER HOSPITALISTS:
A Vital Link in Patient Care

Anup Trikannad, M.D., discusses results with patient Harshad Inamdar.

A strength of the University of Arkansas for Medical Sciences (UAMS) Myeloma Center is the variety of strategies utilized to obtain the best outcome for the patient.

The center's hospitalists are an important part of that process.

The term "hospitalist" was coined in 1996 to describe physicians who only see patients in a hospital, typically treating a variety of conditions. Myeloma Center hospitalists take that one step further.

"There are general hospitalists and myeloma hospitalists. We provide inpatient care for myeloma patients who may be admitted for chemotherapy or related complications," said Anup Trikannad, M.D. "We're a primary care physician while they're in the hospital, but we're more specialized for myeloma."

Myeloma patients are seen by this team even if they're in the hospital for reasons not necessarily related to their condition.

"If a myeloma patient comes to the emergency room or is in the ICU, we still see them," said Tanvi Patel, M.D.

Myeloma treatment presents special challenges, and the concept of hospitalists who focus on myeloma patients is a plus.

"It's a team effort," said Hira Imad Cheema, M.D. "We learn every day from the oncologists on how to help take better care of myeloma patients."

"We have constant discussions with the oncologists, so they are aware of what's going on with their patients," added Asis Shrestha, M.D.

Myeloma Center hospitalists conduct the actual stem cell infusion procedures in both inpatient and outpatient settings, and follow these patients till they recover from the side effects.

Trikannad said there are various scenarios where a patient could be admitted under the care of the hospitalists.

"A patient may be newly diagnosed with myeloma. They have a workup done and maybe they're a candidate for a stem cell transplant," he said. "If it is felt they need to be in the hospital, we take them."

"We get patients from the Outpatient Clinic to the hospital," Trikannad continued. "We also take patients from Infusion B who may need to be admitted so we have some continuity of care."

Cheema said patients greatly benefit from of the team's general medical knowledge.

"Our inpatient and internal medicine training helps," she said. "We can not only take care of the oncology side, but any other issues a patient may have."

While the Myeloma Center hospitalists aren't oncologists, training in that field is a key element in treating myeloma patients at UAMS.

"It's a continuing learning process with myeloma," said Shrestha. "We have discussions and meetings with the oncologists."

"We're always learning," Cheema said. "Before we start taking care of any of the myeloma patients, we go through training provided by the oncologists."

Patel notes how understanding myeloma treatment assists in their work with those patients.

"If we know what kind of treatment a patient has received, such as whether they've had any recent transplants or what specific type of therapy they're on, that helps us make decisions on how to treat other issues," she said.

Myeloma patients undergoing immunotherapy or cellular therapy can experience various side effects, including cytopenia, infections or mucositis. A common side effect for myeloma patients is cytokine release syndrome (CRS). The symptoms of CRS can be similar to those of an infection, so it's important for the hospitalists to know the patient's treatment regimen.

"If a patient has had an immunotherapy treatment and presents with a fever within

"We're a primary care physician while they're in the hospital, but we're more specialized for myeloma."

"We're very coordinated, from the social workers, the nursing staff and the oncologists."

a few days, there's a good chance it's CRS," said Shrestha. "If it's beyond that point, an infection is the more likely cause."

The hospitalists stress the importance of communicating with the rest of the care team.

"Our communication works very well," Patel said. "If a myeloma patient is admitted, we inform the oncologist."

"We have weekly meetings about our patients, and the oncologists help direct us," Trikannad said.

"It's important to have that contact with the patient's oncologist so we can inform them of what's going on while they're in the hospital," Cheema said.

"We're very coordinated, from the social workers, the nursing staff, and the oncologists," Shrestha added. "We want the best for our patients."

Trikannad expressed the overriding feeling about the team.

"We take accountability for any myeloma patient — they're ours," he said.

our hospitalists

Hira Imad Cheema, M.D.

Manozna Karri, M.D.

Syed Naqvi, M.D.

Tanvi Patel, M.D.

Asis Shrestha, M.D.

Amip Trikannad, M.D.

Bispecific BCMA/CD24 CAR T cells control multiple myeloma growth

Nature Communications
January 2024
Primary authors: **Fumou Sun, M.D.; Yan Cheng, M.D.**

Anti-multiple myeloma B cell maturation antigen (BCMA)-specific chimeric antigen receptor (CAR) T-cell therapies represent a promising treatment strategy with high response rates in myeloma. However, durable cures following anti-BCMA CAR T-cell treatment of myeloma are rare. One potential reason is that a small subset of minimal residual myeloma cells seeds relapse. Residual myeloma cells following BCMA-CAR-T-mediated treatment show less-differentiated features and express stem-like genes, including CD24. CD24-positive myeloma cells represent a large fraction of residual myeloma cells after BCMA-CAR-T therapy. In this work, we develop CD24-CAR-T cells and test their ability to eliminate myeloma cells. We find that CD24-CAR-T cells block the CD24-Siglec-10 pathway, thereby enhancing macrophage phagocytic clearance of myeloma cells. Additionally, CD24-CAR-T cells polarize macrophages to a M1-like phenotype. A dual-targeted BCMA-CD24-CAR-T exhibits improved efficacy compared to monospecific BCMA-CAR-T-cell therapy. This work presents an immunotherapeutic approach that targets myeloma cells and promotes tumor cell clearance by macrophages.

Teclistamab in relapsed refractory multiple myeloma: multi-institutional real-world study

Blood Cancer Journal
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Primary authors: **Meera Mohan, M.D.** (Medical College of Wisconsin); **Jorge Monge, M.D.** (Weill Cornell Medicine); **Nishi Shah, M.D.** (Montefiore-Einstein).
Supervisory author: Carolina Schinke, M.D. (UAMS College of Medicine)

The objective of our study was to report real-world data on the safety and efficacy of standard-of-care teclistamab in patients with relapsed/refractory multiple myeloma (MM). This is a multi-institutional retrospective cohort study and included all consecutive patients that received at least one dose of teclistamab up until August 2023. One hundred and ten patients were included, of whom, 86% had triple-class refractory disease, 76% penta-refractory disease, and 35% had prior exposure to B-cell maturation antigen (BCMA)-targeting therapies. The overall response rate (ORR) in our cohort was 62%, with a ≥ very good partial remission (VGPR) rate of 51%. The ORR in patients with and without prior BCMA-targeted therapies was 54% versus 67%, respectively ($p = 0.23$). At a median follow-up of 3.5 months (range, 0.39–10.92), the estimated 3-month and 6-month progression free survival (PFS) was 57% (95% CI, 48%, 68%) and 52% (95% CI, 42%, 64%) respectively. The incidence of cytokine release syndrome (CRS) and immune effector cell associated neurotoxicity syndrome (ICANS) was 56% and 11% respectively, with grade ≥3 CRS and ICANS noted in 3.5% and 4.6% of patients respectively. Seventy-eight unique infections were diagnosed in 44 patients, with the incidence of all-grade and grade ≥3 infections being 40% versus 26% respectively. Primary prophylaxis with intravenous immunoglobulin (IVIG) was associated with a significantly lower infection risk on multivariate analysis (Hazard ratio [HR] 0.33; 95% CI 0.17, 0.64; $p = 0.001$). The main message is that all patients who receive teclistamab should receive prophylactic IvIG to mitigate the risk of infection.

UAMS
Myeloma Center

4301 West Markham #816
Little Rock, AR 72205-7199

behind the scenes

Visanu Wanchai, Ph.D.

Visanu Wanchai, Ph.D., is a postdoctoral fellow with the UAMS College of Medicine. He earned his doctorate in biomedical informatics from UAMS in 2020 and joined the Myeloma Center in 2022.

His focus is developing leading-edge computational tools and employing high-performance computing techniques for single cell analysis to investigate key genes and regulatory mechanisms involved in cancer cell development and resistance to therapy.

Wanchai earned an American Society of Hematology (ASH) Abstract Achievement Award and was a presenter at the 65th ASH Annual Meeting in San Diego in December 2023. He earned his bachelor's degree in computer science at Mae Fah Luang University in Thailand and his master's degree in bioinformatics and systems biology at King Mongkut's University of Technology Thonburi in Thailand.

Zijun Zhang, M.S.

Zijun Zhang, M.S., is a graduate student in the UAMS College of Medicine Department of Biochemistry and Molecular Biology pursuing a Ph.D. in biomedical sciences. He began his studies at UAMS in August 2021 and joined the Myeloma Center as a research assistant in February 2022.

Zhang analyzes CST6, a protein inhibitor found in some multiple myeloma patients. CST6 can plays a positive role by inhibiting bone disease but can also suppress the immune system in the bone marrow microenvironment. Zhang has generated three mutants of CST6 during his research. One of these mutants does not cause immune suppression and still has a positive effect on the bone. Such beneficial proteins can be carried to the bone marrow by chimeric antigen receptor (CAR) T cells.

He earned his bachelor's degree in biochemistry and master's degree in pharmacology from the University of Minnesota Twin Cities.