Carfilzomib Can Lead to Cardiovascular Toxicity in Multiple Myeloma

The proteasome inhibitor carfilzomib has taken on an increasing role in the treatment of multiple myeloma, but new research from the Abramson Cancer Center of the University of Pennsylvania shows the therapy comes with the risk of cardiovascular problems in a higher than expected percentage of patients. An analysis of past studies shows 18 percent of multiple myeloma patients receiving carfilzomib experience cardiovascular adverse events (CVAE) such as hypertension, heart failure, heart attacks, or arrhythmia. More than eight percent of patients experience high-grade CVAEs that are more severe, which is more than twice as common as with other drugs for treating relapsed myeloma. Researchers published their findings in JAMA Oncology.

Multiple myeloma (MM) is a bone marrow cancer that affects plasma cells. Normal plasma cells work as part of the immune system, but in MM these cells become cancerous and grow out of control, leading to multiple painful bone tumors, as well as anemia, kidney failure, and recurrent infections. The American Cancer Society estimates there were more than 30,200 new cases of MM in 2017. Standard treatments include chemotherapy and radiation. Survival of these patients has improved with the use of proteasome inhibitors.

Carfilzomib is one of three proteasome inhibitors currently approved for use by the U.S. Food and Drug Administration. Proteasomes are essentially garbage workers that break down and eliminate proteins inside a cell. Diseases that require more protein turnover to survive, like MM, need more proteasomes. The inhibitor drugs block them from doing their job, causing the cells to fill up with protein and die.

“Like any cancer therapy, the concern with this approach is that it may have an effect on an otherwise healthy part of the body – in this case, the heart,” said the study’s lead author Adam J. Waxman, MD, a Hematology Oncology fellow in the Perelman School of Medicine at the University of Pennsylvania.

Brendan M. Weiss, MD, an adjunct professor of Hematology Oncology at Penn, is the study’s senior author. Weiss also works in research and development at Janssen Pharmaceuticals, which does not manufacture or support any of the drugs involved in this analysis.

Researchers gathered data from 24 studies reported from 2007 through 2017, which included information on 2,594 MM patients. They found 18.1 percent of patients who took carfilzomib experienced CVAE, with 8.2 percent of those cases being grade three or higher, meaning they are categorized as severe. For comparison, a similar review of bortezomib, another proteasome inhibitor, found just 3.8 percent of patients experienced CVAE and only 2.3 percent were severe.

The most common CVAEs were hypertension (12.2 percent) and heart failure (4.1 percent). Arrhythmias (2.4 percent) and ischemic events (1.8) – in which there isn’t enough blood flow to the heart leading to the death of heart muscle – were observed less commonly.

Researchers also found that higher doses of carfilzomib are associated with higher rates of CVAE, and that carfilzomib was associated with an elevated risk of CVAE compared to control groups who did not receive carfilzomib.

“Taken together, these findings argue that carfilzomib is responsible for an elevated risk, and anyone who is treating patients with this drug needs to be aware that this is a common event,” Waxman said.

Researchers say these findings are particularly important since there are already overlapping risk factors for both MM and cardiovascular disease, such as older age and obesity. Previous studies have shown nearly two-thirds of MM patients had cardiovascular disease at baseline, and 70 percent experienced cardiovascular events within six years.

“Clinicians should be paying attention to who may be at highest risk for these events so they can tailor their therapy accordingly,” Waxman said.

Publication: JAMA Oncology
Source: Penn Medicine Communications
Contact: John Infanti, john.infanti@uphs.upenn.edu
FDA Approves Olaparib for Patients with BRCA Breast Cancer

Great news last week that the FDA approved the PARP inhibitor olaparib for patients with metastatic BRCA mutant breast cancer, based on a phase III NEJM study co-led by Susan Domchek, MD at the ACC and the Basser Center for BRCA, and colleagues across the country.

The approval is significant not only as the first specific therapy for BRCA mutation carriers with breast cancer, but also represents a new option, better than chemotherapy, for 10% of all patients with metastatic triple negative cancer.

For months, the Penn Center for Personalized Diagnostics has already been providing BRCA testing of tumors, putting Penn in a leading position to identify patients who would benefit and to offer this therapy immediately (Precision Medicine!). Scientists at the Basser Center including Katherine Nathanson deputy director of the ACC, and Roger Greenberg, co-Leader of the ACC Breast Cancer Research Program, as well as Eric Brown, Ronny Drapkin, Fiona Simpkins, Kara Maxwell, Payal Shah, and Kim Reiss-Binder are working hard to reveal the underlying biological mechanisms of PARP inhibition.

In 2011, representing Penn, Dr. Domchek published an open letter with an international group of clinicians in the Journal of Clinical Oncology calling out the need to do this study when pharma had appeared to put these drugs on the shelf for this indication. Investigator after investigator, the ACC is dedicated to hope and progress.

“It is so thrilling that ‘Penn’ and ‘FDA approval’ are being heard together again and again these past few months,” said Robert Vonderheide, MD, DPhil, ACC Director. “This represents great progress for our patients. And in the very moment of celebration, we recognize how much more work there is to do, so we will be relentless.”

Penn/Virtua Alliance Brings Proton Therapy to South Jersey

Cancer care in South Jersey is about to enter a new era. Penn Medicine, in partnership with Virtua, announced plans to build a new proton facility on the campus of Virtua’s acute care hospital, Virtua Voorhees. The new $35 million center, which will allow cancer patients to undergo cutting edge proton therapy in single-room treatments, is expected to be completed by 2020. It will be the first and only proton therapy center in South Jersey.

“Penn has established itself as a global leader in proton therapy both for the treatment of patients and the training of other medical professionals, and now we’re excited to spread that expertise to residents of South Jersey,” said Ralph Muller, CEO of the University of Pennsylvania Health System. “In partnership with Virtua, this center will usher in a new era of cancer treatment in South Jersey and give patients access to cutting edge care without having to come to Pennsylvania.”

Proton therapy has a few key differences from traditional radiation. Traditional therapy uses x-rays, which are a form of photon radiation. The rays go into the body from one side and come out the other, touching more than just the cancer cells and potentially damaging healthy tissue along the way. The proton beam is positively charged and enters the body at a low dose of radiation. When it hits the cancer it’s targeting, the dosage increases. The beam then stops, preventing the radiation from moving through healthy tissue and exiting the other side of the body. This allows healthy tissue to be spared, while maximizing the chances of attacking cancer cells.

Penn Medicine is a global leader in proton therapy. Penn radiation oncologists have treated almost 4,500 patients since the Roberts Proton Therapy Center first opened in 2010, and have trained more than 500 medical professionals from across the world, many of whom attend an annual three-day course hosted at Penn. That course helps train doctors and health care leaders to learn about best practices in the use of this emerging technology as they establish new proton centers around the world. Clinical trials in the Roberts Proton Therapy Center have mapped new treatments for pediatric brain and spinal cord tumors, pancreatic cancer, lung cancer and many other diseases which are otherwise difficult to treat with radiation. Now that global expertise will bring state-of-the-science proton therapy to the South Jersey community.

“Currently, patients who may benefit from proton therapy – especially for hard-to-treat cancers – can only receive this therapy at a handful of specialized centers across the country,” said James M. Metz, MD, chair of Radiation Oncology at Penn. “This project represents the next phase of proton therapy, in which these treatment facilities will spread into the community to make it easier for patients to get access, and Penn is proud to once again lead the way.”

(Continued on page 4)
Seminars and So Forth

Tuesday 1/16/18
12:00 pm
Distinguished Lecture in Cancer Research
"Unraveling mechanisms of signal transduction."
Stephen Blacklow, MD, PhD, Professor, Cancer Biology, Dana-Farber Cancer Institute; Chair, Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School
BRB II/III Glen Gaulton Auditorium

Tuesday 1/16/18
3:30 pm
Biostatistics Seminar Series
"Methods for Evaluating the Time-Varying Prognostic Performance of Survival Models." C. Jason Liang, PhD, Mathematical Statistician, Biostatistics Research Branch, Div. of Clinical Research, NIAID
701 Blockley Hall

Tuesday 1/16/18
4:00 pm
Immunology Colloquium
"Functions and diseases of the resident macrophage lineage." Frederic Geissmann, MD, PhD, William E. Snee Chair of Immunology, Memorial Sloan Kettering Cancer Center
CRB Austrian Auditorium

Wednesday 1/17/18
12:00 pm
Microbiology Seminar Series
"Autophagy manipulation by intracellular pathogens." Craig Roy, PhD, Waldemar Von Zedtwitz Professor of Microbial Pathogenesis and of Immunology; Vice-Chair, Department of Microbial Pathogenesis, Yale University
CRB Austrian Auditorium

Wednesday 1/17/18
12:00 pm
CRRWH Seminar Series
"Delineating the differential impact of Poly ADP-ribosylpolymerase (PARP) inhibition on ovarian cancer cell subpopulations: Identifying a potential mechanism of resistance." Bo R. Rueda, PhD, Associate Professor, Obstetrics, Gynecology and Reproductive Biology, Harvard Medical School; Director, Vincent Center for Reproductive Biology, Massachusetts General Hospital
Room 251 BRB II/III

Thursday 1/18/18
3:00 pm
Mari Lowe Comparative Oncology Seminar
"Extracellular miRNAs: A Remote Effect of Cancer." Emily Wang, PhD, Associate Professor, Department of Pathology, UC San Diego
132 Hill Pav., Penn School of Veterinary Medicine

Monday 1/22/18
11:00 am
CHOP Path & Lab Faculty Candidate Seminar
"Rendering the metabolic architecture of the immune system with reverse genetics." Will Bailis, PhD, CRI Irvington Postdoctoral Fellow, Yale School of Medicine
CRB Austrian Auditorium

Monday 1/22/18
12:00 pm
IRM Distinguished Seminar Series
"Capturing tissue dynamics and functions by live imaging." Valentina Greco, PhD, Associate Professor of Genetics and of Dermatology and Cell Biology, Yale University
BRB II/III Auditorium

Tuesday 1/23/18
12:00 pm
Distinguished Lecture in Cancer Research
"Oncogenic Ras-dependent determinants of tumor fitness." Dafna Bar-Sagi, PhD, Professor of Biochemistry; Vice Dean for Science and Chief Scientific Officer PhD, Kimmel Center for Stem Cell Biology, NYU Langone
Caplan Auditorium, 37th & Spruce Sts. (Wistar)

Tuesday 1/23/18
4:00 pm
Immunology Colloquium
"Gene conversion and somatic hypermutation in murine and human B cells." Joshy Jacob, PhD, Associate Professor, Department of Microbiology and Immunology, Emory University School of Medicine
CRB Austrian Auditorium

Tuesday 1/23/18
4:00 pm
CHOP CCCR Oncology Seminar Series
"Quantitative Proteomics for Understanding Modified Proteins and Proteomes." Benjamin A. Garcia, PhD, Professor of Biochemistry and Biophysics, Director of Quantitative Proteomics, Penn Epigenetics Institute, Department of Biochemistry & Biophysics, PSOM
CTRB 1200B (CHOP)

Thursday 1/25/18
12:00 pm
Radiation Oncology Seminar Series
Eddy S. Yang, MD, PhD, Professor of Radiation Oncology, University of Alabama-Birmingham
CTRB 8-146AB

Friday 1/26/18
8:00 am—4:00 pm
2018 Update in Hematologic Malignancies CME
This CME/CNE conference is a comprehensive review of hematologic malignancies focusing on the clinical application of new research developments over the preceding year. Details & registration.
Hilton Philadelphia City Avenue
Funding Opportunities

**ConPAR-18-560 NCI Investigator-Initiated Early Phase Clinical Trials for Cancer Treatment and Diagnosis (R01)**

**LOI Deadline:** 30 days prior to the application due date

**Application Deadline:** February 15, 2018

The purpose of this FOA is to seek research projects that implement early phase (Phase 0, I, and II) investigator-initiated clinical trials focused on cancer-targeted diagnostic and therapeutic interventions of direct relevance to the research mission of the National Cancer Institute's (NCI) Division of Cancer Treatment and Diagnosis (DCTD). Applicants are strongly encouraged to consult the [NCI DCTD website](https://grants.nih.gov/grants/guide/pa-files/PAR-18-560.html) at to learn more about the various program goals, research priorities, and strategies developed to fight cancer.

**PAR-18-559 Cancer Prevention and Control Clinical Trials Grant Program (R01)**

**LOI Deadline:** 30 days prior to the application due date

**Application Deadline:** February 15, 2018

Through this FOA, the National Cancer Institute (NCI) invites applications for support of investigator-initiated clinical trials that have the potential to reduce the burden of cancer through improvements in early detection, prevention, healthcare delivery, quality of life, and/or survivorship related to cancer; with such attributes, the proposed studies should also have the potential to improve clinical practice and/or public health.


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**Penn/Virtua Alliance**

(Continued from page 2)

“This highly sophisticated cancer treatment will be available to South Jersey residents as a result of the strong partnership between Virtua and Penn Medicine,” said Dennis W. Pullin, FACHE, Virtua President and CEO. “The outstanding value for our patients is that they will receive advanced cancer care close to home and family, with radiation treatment plans developed by Penn's radiation oncologists.”

From evaluation to treatment, patients will be able to get everything they need at the new facility, including access to clinical trials involving proton therapy. The aspect of care that will remain centered at Penn Medicine is the treatment planning phase, which will be done virtually, providing patients with access to Penn's expertise without having to come into Philadelphia for their appointments.

“We have almost a decade of experience in this field that we will continue to lean on, and keeping the treatment planning centralized will ensure that all of that expertise moves seamlessly into the community,” Metz said. “For patients, it will be the same experience they would get on Penn’s campus.”

The Penn Medicine/Virtua strategic alliance creates easier access to advanced specialty care by growing programs in South Jersey supported by both organizations. With an understanding that patients want to be close to home and family when dealing with serious illnesses, this partnership provides the best plan of care that incorporates facilities in both health systems. Virtua continues to explore collaboration opportunities with Penn Medicine to strengthen and support Virtua’s delivery of specialty care. The alliance reduces duplication of resources, increases efficiency, and enhances convenience for patients and families. It fosters relationships among the medical professionals of both organizations, ensuring delivery of care in the appropriate setting, eliminating gaps in care and improving access to specialty services.

Source: Penn Medicine Communications
Contact: John Infanti, john.infanti@uphs.upenn.edu