MedicalXpress

Carfilzomib can lead to cardiovascular toxicity in multiple myeloma patients

December 28 2017

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 today 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.

Researchers also called for further clinical trials to specifically evaluate this connection, arguing that it may be underrepresented by current data.

"If you're not specifically looking for this, you might report it differently," Waxman said.

More information: *JAMA Oncology* (2017). DOI: 10.1001/jamaoncol.2017.4519

Provided by Perelman School of Medicine at the University of Pennsylvania