Combination therapy found to lower blood pressure in patients receiving ibrutinib

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Combination treatments with two or more blood pressure drugs can significantly reduce blood pressure in patients taking ibrutinib, according to a new study published in *Blood Advances.*

Targeted drugs such as ibrutinib have improved outcomes for patients with cancers of the lymphatic system, but patients treated with ibrutinib and other drugs in its class often develop new or worsening high blood pressure (or hypertension or HTN). Few studies have examined how best to treat this potentially serious side effect, nor do any formal guidelines exist to steer doctors toward the most effective treatments.

"To our knowledge, this is the first and only study to examine how to optimally treat high blood pressure in patients receiving ibrutinib," said Mazyar Shadman, MD, MPH, of Fred Hutchinson Cancer Center and the University of Washington School of Medicine, and the study's senior author. "Our findings strongly suggest that aggressive treatment with certain combinations of antihypertensive medications can achieve significantly reduced blood pressures in this patient population."

The researchers found that different drug combinations may be more effective depending on whether patients had high blood pressure before starting treatment with ibrutinib or developed high blood pressure while taking the drug.

Ibrutinib, which has been on the market since 2013, was the first drug in its class, known as Bruton tyrosine kinase inhibitors (BTKis), to receive U.S. Food and Drug Administration (FDA) approval to treat patients with mantle cell lymphoma, chronic lymphocytic leukemia, and certain other lymphoid cancers.

"Several studies have shown that BTKis can cause patients to develop new or worsening high blood pressure," said Laura Samples, MD, also of Fred Hutchinson Cancer Center and the University of Washington School of Medicine, and the study's first author.

"One study found this to be the case in over 78% of patients treated with ibrutinib over a median of 30 months," Dr. Samples said. "Uncontrolled

high blood pressure, or hypertension, can lead to major adverse cardiovascular events, such as heart attack, heart failure, and stroke."

For this study, Drs. Samples, Shadman, and their colleagues examined the medical records of 196 patients who were concurrently treated with a BTKi and one or more antihypertensive medication for at least three months between 2014 and 2018 at one of 14 medical centers in the United States.

Nearly 93% of the study's participants identified as Caucasian, with an average age of 67 years. Approximately 71% were male, while 29% were female.

The patients were separated into two groups: those who were taking at least one antihypertensive medication before starting treatment with a BTKi (the prior-HTN group; 118 patients) and those who began taking one or more antihypertensive medications while being treated with a BTKi (the group that developed new onset high blood pressure after starting treatment; 78 patients).

The researchers categorized antihypertensive medications into four groups: ACE inhibitors and angiotensin receptor blockers (ARBs), beta blockers, calcium channel blockers, and hydrochlorothiazide. The study's primary outcome was the effectiveness of antihypertensive treatment as assessed by the average reduction in mean arterial pressure (MAP), the average pressure in a patient's arteries during one heartbeat cycle.

Results showed that patients in the prior-HTN group who took beta blockers along with hydrochlorothiazide achieved statistically significant average reductions in MAP of about five mmHg (unit of measurement for blood pressure).

Patients in the de novo HTN group who took ACE inhibitors or ARBs

along with hydrochlorothiazide achieved similar reductions in MAP. Approximately 15% of patients in both groups taking beta blockers and hydrochlorothiazide reached what researchers classified as a normal blood pressure range (120/80 or lower).

"Our results reinforce that—in this patient population as in patients with hypertension in general—you need to treat with multiple drugs to achieve successful blood pressure control," said Dr. Samples.

The study findings do not shed any light on why certain combination regimens were more effective than others or why different combination regimens were most effective in patients with pre-existing and new-onset hypertension, Dr. Shadman added. "But we now have some data that other researchers can analyze to perhaps find answers to these questions," he said.

A limitation of the study is that it is retrospective—that is, it looked back at patients' medical records to determine how they were treated and what the outcomes were.

"Large prospective studies are needed to develop formal guidelines on the most effective antihypertensive regimens in patients taking BTKis," Dr. Samples said.

Secondly, patients' blood pressure was measured only during clinic visits. Studies have shown that blood pressure measurements taken in doctors' offices or other clinical settings can produce varying results.

"Future studies should, if possible, measure patients' blood pressure using wearable devices that measure blood pressure over a 24-hour period," Dr. Shadman said.

Finally, nearly 90% of patients in the study were taking ibrutinib. The

rest were treated with acalabrutinib or other, newer BTKi's such as zanubrutinib, which received its initial FDA approval in 2019. Data for the study came from a period when ibrutinib was still more common than its second-generation counterparts.

"Studies suggest that patients taking these newer agents still face an increased risk of major adverse cardiovascular events, although the risk may be lower than that of ibrutinib," Dr. Samples said.

"Given that increased blood pressure is a 'class effect' of treatment with BTKis, both doctors and patients need to be aware of this risk and patients' blood pressure should be monitored regularly so that treatment can begin immediately when an increase is detected," Dr. Samples said.

More information: *Blood Advances.*

Provided by American Society of Hematology