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# Combination of 2 novel anti-cancer agents may help fight CML resistant to current therapy

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Virginia Commonwealth University Massey Cancer Center researchers have identified that a combination of novel anti-cancer compounds is able to kill chronic myelogenous leukemia cells previously resistant to conventional forms of therapy.

Chronic myelogenous leukemia, or CML, is a cancer of the bone marrow caused by a specific genetic abnormality and is one of the more common forms of leukemia. Imatinib mesylate, or Gleevec, is a highly effective anti-cancer agent that has revolutionized the course of therapy for patients with CML. It works by inhibiting the activity of a mutant protein, known as Bcr/Abl, which is responsible for the disease. However, despite initial success, patients eventually become resistant to imatinib mesylate, often through the development of further mutations in the Bcr/Abl protein.

According to Steven Grant, M.D., Massey's associate director for translational research and co-leader of the cancer center's cancer cell biology program, and senior author of the study, resistance to imatinib mesylate prompted the search for newer agents that are active against the mutated forms of Bcr/Abl. Such agents include MK-0457, a Bcr/Abl kinase inhibitor that also targets another protein called an aurora kinase. Aurora kinase plays an important role in mitosis and cell division. In preclinical studies, MK-0457 is active against the T315I Bcr/Abl mutation, a major cause of imatinib resistance, and has shown promise

in early clinical trials, Grant said.

In this study, Grant and colleagues examined the effects of combining MK-0457 with vorinostat, a novel targeted agent that has recently been approved for the treatment of cutaneous T-cell lymphoma. They found that this combination leads to a dramatic induction of apoptosis, or programmed cell death in CML cells, including imatinib-resistant cells bearing the T315I or other mutations. The article was pre-published as a First Edition Paper in Blood, the journal of the American Society of Hematology, which appeared online May 27.

Further, Grant said that the interaction between these agents may occur at multiple levels, including potentiation of Bcr/Abl inhibition as well as enhanced disruption of aurora kinase and mitosis. In addition, the group demonstrated that vorinostat-mediated up-regulation of Bim, a pro-apoptotic protein, contributed significantly to the effectiveness of this regimen.

“Our findings suggest it may be possible to develop a clinical regimen combining a third-generation Bcr/Abl kinase and aurora kinase inhibitor, such as MK-0457, with histone deacetylase inhibitors, such as vorinostat,” Grant said.

“Theoretically, this combination could improve upon the results of Bcr/Abl kinase inhibitors administered alone, particularly in the case of imatinib-resistant disease,” he said. Further preclinical studies are underway to test this hypothesis.

Source: Virginia Commonwealth University